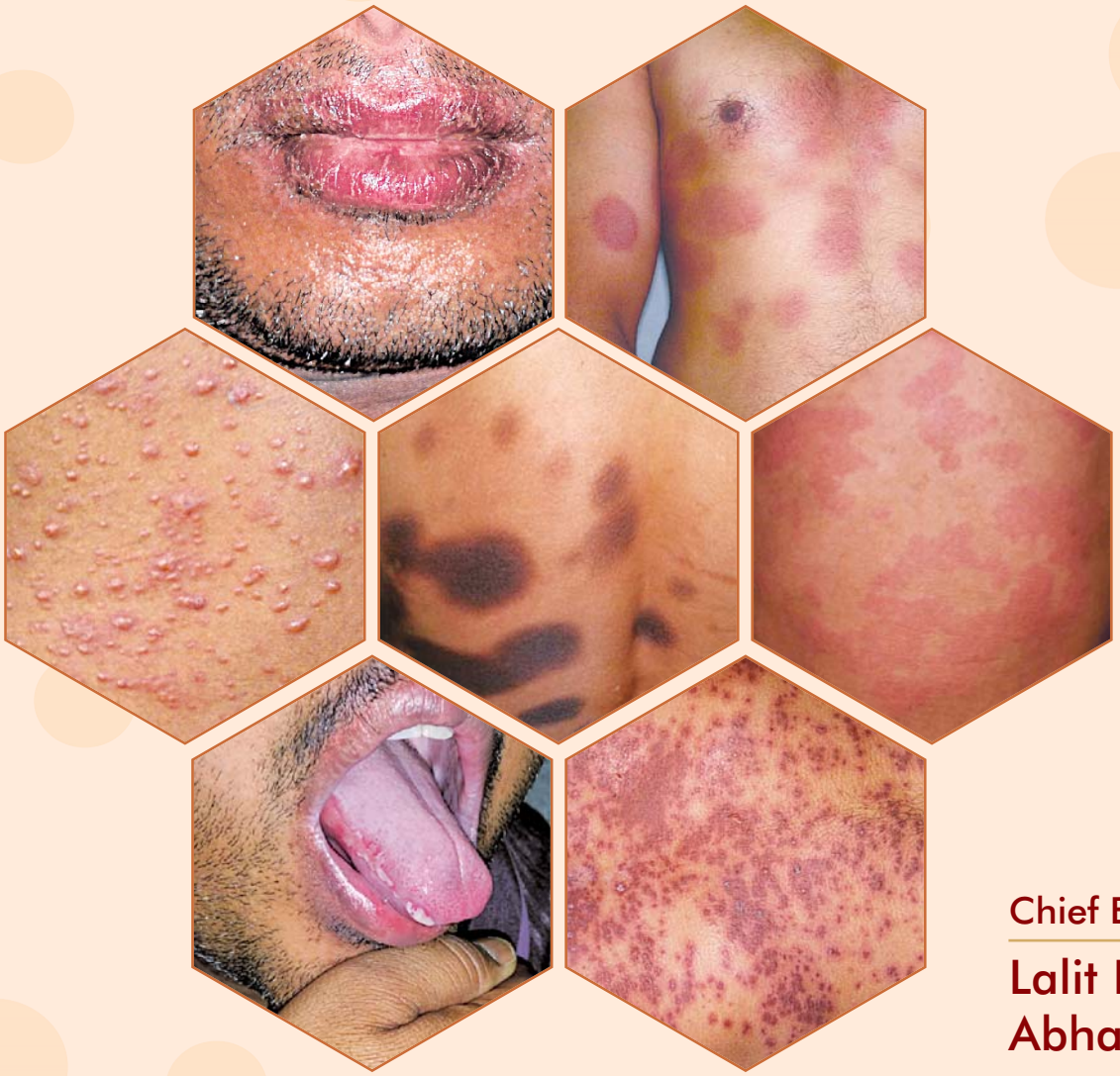
IADVL's Textbook on

CUTANEOUS ADVERSE DRUG REACTIONS

A Comprehensive Guide



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BHALANI

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Dedicated

To

Our Teachers

For nurturing our academic aspirations

Our Parents

For their blessings and affection

Our Wives and Children

Dr. Anjana, Sujay and Vartika (Lalit Kumar Gupta)
Dr. Anju Chacko, Diya and Ria (Abhay Mani Martin)
Dr. Maria, Jeanne and Stephen (Paschal D'Souza)
Mrs. Shraddha, Shambhavi and Shiven (Sushil Pande)

For their understanding, forbearance and unconditional support

Our Patients

For providing us an opportunity to serve them and learn from them in return

Foreword

Nothing seems as straightforward as the story of a drug reaction. You are prescribed a medication for an illness and develop a reaction soon afterwards; the causative medication is identified and stopped; treatments are given and you get better; you never take the medication again and stay well for the rest of your life. Depending on the cultural beliefs of your community, you may regard the doctor who gave you the medication with varying degrees of dislike and also think poorly of the system of modern medicine he practices. You may be better disposed to the doctor who diagnosed your drug reaction and got you better, if he or she is a different person. You may be given a list of drugs to avoid and others that are safe for you. And that is the end of the story, slightly unpleasant but ending well.

However, anybody with experience in this field is struck by the extent of uncertainty that dogs every step of the process of diagnosing, treating and preventing drug reactions. Not every reaction that develops in a person taking a drug is a drug reaction. When many drugs are taken together, or one after another, knowing which one caused the reaction is not easy and sometimes non-prescription drugs and substances, taken by any route, may be responsible. The time between taking a drug and developing a reaction may vary from a few minutes to several days and even up to a few weeks. Once in a while, a drug taken safely for long may produce a reaction.

An additional complication arises when patients do not know or remember the medications they were taking or only have loose samples of the drug they were given by a health care provider, medical shop clerk or a friend. Even when patients are carrying their prescriptions, it may be difficult to know which drugs they were taking because of the multiplicity of brand names in our country, changing every 100 km or so without any central, consolidated record of the various names.

In many people, stopping the suspected medication is not an easy option as it may be crucial to their health and finding a safe and effective substitute may be difficult. There are no tests that can quickly and reliably indicate which drug caused a reaction and which drug is safe to administer.

Prescription practices are a major determinant of the prevalence and cause of drug reactions. However, some drugs are more prone to provoking reactions than others and some people are more prone to developing reactions than others. Some people react to multiple drugs, or believe they do. Interestingly, the same drug may cause different kinds of reactions in different people. Other agents, including viruses, sunlight and pre-existing disease and its treatment may influence the development, duration or recurrence of a drug reaction. There are explanations for some of these phenomena but several others are poorly understood. There is also controversy over how to treat a drug reaction with views of appropriate intervention ranging from supportive care alone to aggressive immunosuppression.

As an aside, impoverishment is an important adverse drug reaction that is well documented in the sociology and economics literature and the lay press but does not receive the attention it deserves in the medical literature. On the contrary, doctors and patients are made to believe that enough is not being done if the newest and most expensive medications are not deployed for treatment and that expensive branded medications are better than their cheaper versions.

Basic research into the mechanisms of drug reaction continues with more than one theory considered to be currently valid and several others having fallen along the wayside in the march of time. However, basic work has not shed sufficient light to illumine clinical practice as of now.

Yet amidst this uncertainty, action has to be taken, decisions to be made, interventions to be planned, and often quite quickly. Though drug reactions may affect every organ system, a dermatologist is often considered the appropriate person for the problem and may be consulted to confirm or refute the diagnosis or may be the one to recognize an overlooked diagnosis.

The editors and authors have done an excellent job of preparing a resource that can be consulted by those wanting to learn about drug reactions, not merely in India but around the world. The book covers a lot of ground. As would be expected from a group of dermatologists (the core editorial team belongs to

the special interest group of the Indian Association of Dermatologists, Venereologists and Leprologists), there are detailed descriptions of the clinical manifestations not only in the skin but also in the mucosae, hair and nails. These are well illustrated with several images of high quality. Extracutaneous, systemic manifestations which often accompany severe drug reactions are also covered in sufficient detail. There are descriptions of drug reactions in groups with special features and vulnerabilities such as children, pregnant and lactating women and a large section of the book deals with reactions to specific therapeutic classes of drugs. Rare reaction patterns, drug interactions and legal issues also receive attention.

Treatment depends on the severity and type of drug reaction and this is covered in considerable detail providing insights and opinions on controversial areas. While the task of helping the affected patient is more immediate and urgent, the responsibility to the larger community is emphasized in the section on pharmacovigilance which describes how to report drug reactions to the appropriate agencies using simple and quick processes. The book also describes the aetio-pathogenesis of drug reactions as currently understood. While addressing nearly all of the multiple issues related to the topic, the authors have clearly indicated what is known and what is not, what is well understood and what requires further work and what action to take that will help patients.

I am confident the book will serve the needs of all those who would like to learn about the current state of the field of drug reactions, be they students, physicians or researchers.

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Presidential Messages

It is a matter of huge satisfaction that after tremendous hard work, the book, "**IADVL's Textbook on Cutaneous Adverse Drug Reactions: A Comprehensive Guide"** is ready to be released at Dermacon 2018 at Kochi.

This wonderful resource book encompasses current knowledge on the subject and has an impressive layout. The book with 52 chapters, divided into four sections has dealt with this pertinent topic of Cutaneous Adverse Drug Reactions comprehensively. The book is relevant and up-to-date on aspects like epidemiology, pathogenesis, clinical presentations and management. Special focus chapters on drug interactions, scoring systems, multiple drug hypersensitivity syndrome and therapeutic paradox in dermatology add much value to this comprehensive book.

I congratulate the entire editorial team and all authors for the herculean task and wish that all dermatologists and physicians, not only from India but other countries too, will find it very useful.

Long Live IADVL!!

Lucknow, December 2017

Devesh Mishra
National IADVL President. 2016

I am immensely pleased to note that the long cherished dream of a book on cutaneous adverse drug reactions **"IADVL's Textbook on Cutaneous Adverse Drug Reactions: A Comprehensive Guide"** has now become a reality. I am privileged to be a witness to the whole process. While going through the drafts, I realized that the project has been very well conceived, meticulously planned and wonderfully delivered.

The textbook is a mini encyclopedia that covers the A to Z of Drug toxicity and cutaneous adverse reactions. The fundamentals, clinical presentations, diagnostic and medicolegal aspects have been thoroughly discussed. This will be a good ready-reckoner for practitioners and academicians alike.

I take this opportunity to appreciate the efforts of Editorial team comprising of Dr. Lalit Kumar Gupta, Dr. Abhay Mani Martin, Dr. Paschal D'Souza and Dr. Sushil Pande.

The success of such an ambitious project depends upon the sincere contributions of the authors. They have done their job very well.

I am sure this will be a benchmark publication of our association.

Congratulations to one and all for their whole hearted participation.

Looking forward to be a part of the book release at DERMACON 2018.

Best wishes.
Let us create brilliance together.

Vadodara, December 2017

Yogesh S. Marfatia
National President, IADVL (2017)

Message from IADVL Academy

The **"IADVL Textbook on Cutaneous Adverse Drug Reactions: A Comprehensive Guide"** is one more project initiated by the IADVL Academy as a Presidential project. The editors and authors were selected on the basis of their knowledge and experience in the subject. We are happy to say that this comprehensive yet succinct book has fulfilled our association's aim of providing physicians with the knowledge to recognize and manage cutaneous drug reactions. Authored by eminent experts, it has been structured with relevant information on common and uncommon cutaneous drug reactions and with suitable illustrations. The summary in the beginning of each chapter provides a glimpse of the content, while the learning essentials at the end are very clear pinpoint messages to be remembered. All key information is very well tabulated. The editorial team and authors deserve to be congratulated for bringing out this elucidative book.

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Preface

Drug reactions are a common accompaniment of drug administration. With increasing number of drugs being added to the clinician's armamentarium, the subspecialty of drug reactions has become a keen area of interest to all physicians. Adverse drug reactions (ADRs) are one of the major preventable public health problems. They are common, underreported and an under-recognized cause of morbidity and mortality.

Patients are on multiple drugs for multiple comorbidities and several new drugs are being introduced into the market. Increased longevity and better access to health care facilities make the aging population increasingly exposed to medications and thereby vulnerable to develop adverse drug reactions. Polypharmacy, tendency to consume medication for minor ailments, ignorance of the dangers of taking unsupervised medications coupled with easy availability of over the counter medications in the Indian subcontinent are some of the other causes for increased prevalence of drug reactions.

Skin is one of the most common organ systems affected in drug reactions. Cutaneous ADRs are easily visible to the naked eye and have distinct morphologic patterns. This aids early recognition and prompts rapid withdrawal of the drug and thus averts considerable mortality and morbidity to the patient. Hence, an awareness of the common cutaneous ADRs (CADRs) is an essential prerequisite for any practicing physician. Cutaneous adverse drug reactions can have varied presentations and may mimic almost any inflammatory dermatosis. Fortunately most reactions are benign and do not cause significant complications and sequelae. However, a few reactions like toxic epidermal necrolysis, Stevens-Johnson syndrome, drug hypersensitivity syndrome, erythroderma and vasculitis may have serious consequences and may result in significant mortality if not managed promptly..

"Medicine is a science of uncertainty and art of probability" said William Osler. Nowhere is this aphorism true than in recognizing drug reactions. A strong clinical suspicion in an appropriate setting, a thorough and meticulous history, temporal correlation between the appearance of rash and introduction of drug, effect of de-challenge and re-challenge are some of the key points in the evaluation of any patient with a suspected drug reaction. Since there are no reliable in-vivo or in-vitro laboratory tests, the diagnosis, even to this day, largely depends on the clinician's acumen and judgment.

A textbook dealing with the scenario of cutaneous ADRs in the Indian subcontinent was a long felt need and **"IADVL's Textbook on Cutaneous Adverse Drug Reactions: A Comprehensive Guide"** is an attempt to fill this gap. It aims to sensitize and guide the clinicians on the practical aspect of management and prevention of ADR in their real life situations.

The textbook is divided into four broad sections— introduction and basics of understanding drug mechanisms, common drug reaction patterns including serious and non-serious reactions, specific reaction patterns to different classes of drugs and drug reactions in some special groups and situations. A chapter on drug-drug interaction is also included and covers the most common and serious drug interactions of practical relevance to dermatologists. A unique chapter on unusual and uncommon drug reactions has been added in the form of "case snippets" to make the readers familiar with rare and bizarre presentations and to enhance their diagnostic repertoire. Relatively under recognized and under discussed entities like multiple drug hypersensitivity syndrome, social and legal issues and paradoxical drug reactions in dermatology are discussed as separate chapters. Some useful resources on the subject like drug recording proforma, patient and clinician information leaflets highlighting facts and myths about drug reactions and Apps for recording ADRs have been provided as appendices.

The content of the textbook is written in a very simple and concise format with plenty of tables, algorithms and clinical pictures to enhance readability and clarify concepts. This comprehensive treatise, written by experts of national and international repute in the field of ADRs will help the clinician (general practitioners, residents and specialist dermatologists alike) make informed decisions in day-to-day practice. In this modern era when patient safety and quality management systems in healthcare delivery are being given priority, safe handling of drugs and early recognition of ADRs will go a long way in making practice safer for patients and physicians alike. We sincerely hope that readers will find our

endeavor useful in their clinical practice and this textbook will guide them to manage their patients with ADRs effectively. A comprehensive desktop reference on this important area of interest has been long overdue and we hope this book will fill this vacuum.

We welcome your constructive criticism and valuable feedback!

January 2018

Lalit Kumar Gupta
Abhay Mani Martin
Paschal D'Souza
Sushil Pande

Acknowledgment

We owe a great deal of gratitude to the Indian Association of Dermatologists Venereologists and Leprologists (IADVL) Academy, under the stewardship of Dr. Ameet Valia, Dr. Seetharam and Dr. Deepika Pandhi for entrusting us with the responsibility of writing a textbook on this important yet neglected subject.

The Special Interest Group on Adverse drug reactions (SIG-ADR) of IADVL Academy was entrusted the onerous responsibility of developing guidelines for SJS-TEN in the country in 2015 by Dr. Venkatram Mysore and Dr. Rashmi Sarkar (then President and Secretary of IADVL). The formation of the SIG-ADR team became the starting point of this delightful journey. What sparked off as a dream of a few members reached its fruition with sincere and dedicated effort of many in the IADVL circles— academicians, teachers, authors and reviewers.

We are fortunate to have had contributions from eminent authors across India and abroad. They are experts in the field of adverse drug reactions and have taken great pains to write lucid chapters for the book. We immensely thank each one of them for sharing their wisdom and experience.

A dedicated team of reviewers— Dr. Sarita Sasidharanpillai, Dr. Deepika Pandhi, Dr. Feroze Kaliyadan, Dr. Vishalakshi Vishwanath, Dr. Vaishali Masatkar, Dr. Iffat Hassan, Dr. Keshavamurthy Adya, Dr. Ashok Kumar Khare, Dr. Deepthi N.S. and Dr. Riti Bhatia helped us at every step in providing their valuable suggestions and inputs. We are indebted to them for their immense contribution.

“Pictures speak a thousand words.” We sincerely thank all those who have contributed clinical images for the book.

The foreword has been so insightfully penned by Professor M. Ramam from AIIMS, a teacher, orator, writer, editor and a clinician par excellence. His contribution and guidance throughout this project is deeply appreciated.

Our deep sense of gratitude to our esteemed teachers. They instilled confidence and courage in us and motivated us to undertake this mammoth project. Without their blessings we would not have been able to dream of this project!!

We also place on record the cooperation of several faculty members (Prof. Dr. Sugathan, Prof. Dr. A.K. Khare, Dr. Manisha Balai, Dr. Vaishali), colleagues (Dr. Deepthi, Dr. Anisha Asok) and residents of our respective departments (Dr. Rini Makhija, Dr. Ritu Agarwal, Dr. Manju Meena, Dr. Sameeksha Chand, Dr. Neha Yadav, Dr. Priya Choudhary, Dr. Rohini Soni, Dr. Rishi Goel, Dr. Archana Lokhande and Dr. Manasi Shirolikar) in providing us with many innovative ideas, offering critical feedback and helping us in proof reading of the drafts on numerous occasions. A special word of thanks to Mr. Kamal of BMH Kozhikode for his contributions as an artist in designing diagrams and flowcharts in the relevant chapters.

Our family members, parents, spouses and children made countless sacrifices during our mission to complete the task in time and deserve a heartfelt gratitude for their silent and selfless affection, cooperation and contribution.

We thank all our patients who have allowed us to learn so much by being cooperative in spite of their agony and pain.

We thank Almighty God for his benevolence and giving us strength and patience to carry out this mission to the best of our ability.

We are grateful to our Publisher Bhalani Publishing House— Mr. Hemant S. Bhalani, Mr. Himanshu H. Bhalani, Mr. Vishal S. Mayekar and their entire team in pushing us hard to meet the deadlines and for their excellent editorial assistance. We gratefully acknowledge Mr. Ashraf Hussain of Indian Design, Udaipur for designing the cover page.

Editing **IADVL’s Textbook on Cutaneous Adverse Drug Reactions: A Comprehensive Guide** was a thoroughly enjoyable journey and we hope that the readers too will enjoy this. Happy reading!!

Lalit Kumar Gupta
Abhay Mani Martin
Paschal D’Souza
Sushil Pande

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ABBREVIATIONS

6-MP	6-Mercaptopurine
ABC	ATP-Binding Cassette
ACAAI	American College of Allergy, Asthma, and Immunology
ACDR	Adverse Cutaneous Drug Reaction
ACE	Angiotensin Converting Enzyme
ACEI	Angiotensin Converting Enzyme Inhibitors
ACOG	American College of Obstetricians and Gynecologists
ACTH	Adrenocorticotropic Hormone
ADL	Activities of Daily Living
ADME	Absorbed, Distributed, Metabolized, And Excreted
ADRs	Adverse Drug Reactions
AE	Acral Erythema
AED	Antiepileptic Drug
AGEP	Acute Generalized Exanthematous Pustulosis
AIIMS	All India Institute of Medical Sciences
ALDEN	Algorithm of Drug Causality for Epidermal Necrolysis
ALK-1	Activin-Receptor Like Kinase-1
ALL	Acute Lymphocytic Leukemia
AMC	ADR Monitoring Centres
AMDR	Adverse Mucosal Drug Reaction
AMs	Antimalarials
ANA	Antinuclear Antibodies
ANCA	Anti-Neutrophil Cytoplasmic Antibody
ANS	Autonomic Nervous System
APC	Antigen-Presenting Cell
ARB	Angiotensin–Receptor–Blockers
ARDS	Acute Respiratory Distress Syndrome
ART	Antiretroviral Therapy
ATT	Antituberculous Therapy
BAT	Basophil Activation Test
BCG	Bacille Calmette-Guérin
BICU	Burn Intensive Care Unit
BLA	Biologics License Applications
BMR	Basal Metabolic Rate
BMZ	Basement Membrane Zone
BP	Bullous Pemphigoid
BS	Baboon Syndrome
BSA	Body Surface Area
BSACI	British Society for Allergy and Clinical Immunology
CADR	Cutaneous Adverse Drug Reaction
cAMP	Cyclic Adenosine Monophosphate
cART	Combined Antiretroviral Therapy
CBC	Complete Blood Count
CBZ	Carbamazepine
CCB	Calcium Channel Blockers
CDSCO	Central Drugs Standard Control Organization
CDTHL	Chronic Diffuse Telogen Hair Loss
CIBD	Chronic Inflammatory Bowel Disease
CL	Chemical Leukoderma
CML	Chronic Myeloid Leukemia
CMV	Cytomegalovirus
CNS	Central Nervous System
COC	Combined Oral Contraceptives
COX	Cyclo-oxygenase
CPL	Cutaneous Pseudolymphoma
CQ	Chloroquine
CRP	Confluent and Reticulate Papillomatosis
CRP	C-Reactive Protein
CS	Corticosteroids
CsA	Cyclosporine A
CTPL	Cutaneous T-Cell Pseudolymphoma
CYP-450	Cytochrome P-450
DAS-STOP Score	D'souza And Shukla—SJS-TEN Outcome Probability Score
DCGI	Drug Controller General of India
DDS	Diamino Diphenyl Sulfone
DEJ	Dermoepidermal Junction
DHR	Drug Hypersensitivity Reaction
DHS	Drug Hypersensitivity Syndrome
DIBP	Drug-Induced Bullous Pemphigoid
DIC	Disseminated Intravascular Coagulation
DICC	Drug-Induced Cicatrizing Conjunctivitis
DIDMOHS	Drug-Induced Delayed Multiorgan Hypersensitivity Syndrome
DIE	Drug-Induced Exanthems
DIHS	Drug-Induced Hypersensitivity Syndrome
DILABD	Drug-Induced Linear IgA Bullous Disease
DILE	Drug-Induced Lupus Erythematosus
DILI	Drug-Induced Liver Injury
DIP	Drug-Induced Pemphigus
DISCLE	Drug-Induced Subcutaneous Lupus Erythematosus
DLQI	Dermatology Life Quality Index

DMSO	Dimethyl-Sulfoxide
DOAC	Direct Oral Anticoagulants
DPT	Drug Patch Tests
DRBS	Drug Related Baboon Syndrome
DRESS	Drug Reaction with Eosinophilia And Systemic Symptoms
DRESS/DHS	Drug Reaction with Eosinophilia and Systemic Symptoms/Drug Hypersensitivity Syndrome
DTH	Delayed Type of Hypersensitivity
EBA	Epidermolysis Bullosa Acquisita
EBV	Epstein–Barr Virus
EDP	Erythema Dyschromicum Perstans
EECDRG	European Environmental Contact Dermatitis Research Group
EED	Erythema Elevatum Diutinum
EGF	Epidermal Growth Factor
EGFR	Epidermal Growth Factor Receptor
EGFR Inhibitors	Epidermal Growth Factor Receptor Inhibitors
ELISA	Enzyme-Linked Immunosorbent Assay
EM	Erythema Multiforme
EMB	Ethambutol
EMLA	Eutectic Mixture of Local Anesthetics
ENDA	European Network on Drug Allergy
ENDA/EAACI	European Network For Drug Allergy/ European Association Allergy And Clinical Immunology
ENL	Erythema Nodosum Leprosum
EPP	Erythropoietic Protoporphyria
ESCD	European Society of Contact Dermatitis
ESR	Erythrocyte Sedimentation Rate
EU	European Union
Fas-L	Fas Ligand
FDA	Food And Drug Administration
FDE	Fixed Drug Eruption
FDR	Fixed Drug Reaction
FEIA	Fluoroenzyme Immunoassay
FQ	Fluoroquinolones
G6PD	Glucose-6-Phosphate Dehydrogenase
GA	Granuloma Annulare
GABA	γ-Aminobutyric Acid
GBFDE	Generalized Bullous Fixed Drug Eruption
GBHC	Gamma Benzene Hexachloride
G-CSF	Granulocyte-Colony Stimulating Factor
GI	Gastrointestinal
GIST	Gastrointestinal Stromal Tumor
GM-CSF	Granulocyte–Macrophage Colony Stimulating Factor
GnRH	Gonadotropin-Releasing Hormone
GVHD	Graft Versus Host Disease
GWAS	Genome Wide Association Studies
HAART	Highly Active Antiretroviral Therapy
HCPs	Health-Care Professionals
HCQ	Hydroxychloroquine
HCV	Hepatitis C Virus
HER	Human Epidermal Growth Factor Receptor
HER 2	Human Epidermal Growth Factor Receptor 2
HFS	Hand–Foot Syndrome
HFSR	Hand–Foot Skin Reaction
HHV	Human Herpesvirus
HHV-6	Human Herpesvirus-6
HIT	Heparin-Induced Thrombocytopenia
HITT	Heparin-Induced Thrombocytopenia And Thrombosis
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HLA-DR	Human Leucocyte Antigen-Antigen D Related
HLE	Human Leucocyte Elastase
HSR	Hypersensitivity Reactions
HSS	Hypersensitivity Syndrome
HSV	Herpes Simplex Virus
HUMARA	Human Androgen Receptor Gene
IADVL	Indian Association of Dermatologists, Venereologists and Leprologists
ICAM-1	Intercellular Adhesion Molecule 1
ICD	Immunocompromised Districts
ICDRG	International Contact Dermatitis Research Group
ICM	Iodinated Contrast Media
IDT	Intradermal Test
IFN	Interferon
IFN-α	Interferon Alfa
IFN-γ	Interferon Gamma
IGDR	Interstitial Granulomatous Drug Reaction
IGF 1	Insulin-Like Growth Factor 1
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IIF	Indirect Immunofluorescence
IL	Interleukin
IL-2	Interleukin-2
IL-8	Interleukin-8
IM	Infectious Mononucleosis
IM	Intramuscular
IM-ADR	Immune-Mediated Adverse Drug Reactions
INR	International Normalized Ratio
IRIS	Immune Reconstitution Inflammatory Syndrome
ITATSA	IADVL Task Force Against Topical Steroid Abuse

ITP	Immune Thrombocytopenic Purpura
IV	Intravenous
IVIG	Intravenous Immunoglobulin
JHR	Jarisch–Herxheimer Reaction
J-SCAR	Japanese Research Committee On Severe Cutaneous Adverse Reaction
KA	Keratoacanthomas
KS	Kaposi's Sarcoma
LA	Local Anesthetics
LABD	Linear IgA Bullous Dermatosis
LABD	Linear IgA Bullous Disease
LAD	Linear IgA Disease
LCV	Leukocytoclastic Vasculitis
LDIE	Lichenoid Drug-Induced Eruption
LDE	Lichenoid Drug Eruption
LDR	Lichenoid Drug Reaction
LE	Lupus Erythematosus
LFA	Lymphocyte Function–Associated Antigen
LFT	Liver Function Test
LMWH	Low Molecular Weight Heparin
LOS	Length of Stay
LP	Lichen Planus
LST	Lymphocyte Stimulation Tests
LTC4	Leukotriene C4
LTT	Lymphocyte Transformation Tests
MADR	Mucosal Adverse Drug Reactions
MAPK	Mitogen-Activated Protein Kinase
MASCC	Multinational Association of Supportive Care in Cancer
MBH	Monobenzyl Ether Of Hydroquinone
MBMDT	Multibacillary Multidrug Therapy
MDHS	Multiple Drug Hypersensitivity Syndrome
MDIS	Multiple Drug Intolerance Syndrome
MDM	Minor Determinant Mixture
MDS	Myelodysplastic syndrome
MED	Minimal Erythema Dose
MEDRA	Medical Dictionary for Regulatory Activities
MF	Mycosis Fungoides
MHC	Major Histocompatibility Complex
MIARN	Methotrexate-Induced Accelerated Rheumatoid Nodulosis
MiTF	Microphthalmia-Associated Transcription Factor
MKI	Multikinase Inhibitors
MMP	Mucous Membrane Pemphigoid
MPE	Maculopapular Exanthema
MPO	Myeloperoxidase
MSH	Melanocyte-Stimulating Hormone
NCC	National Coordinating Centre
NCI-CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
Nd:YAG	Neodymium-Doped Yttrium Aluminum Garnet
NEH	Neutrophilic Eccrine Hidradenitis
NF-κβ	Nuclear Factor Kappa Beta
NICE	National Institute for Health and Clinical Excellence
NK cells	Natural Killer Cells
NME	New Molecular Entities
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitors
NO	Nitric Oxide
NPFDE	Nonpigmenting Fixed Drug Eruption
NRTI	Nucleoside Reverse Transcriptase Inhibitors
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
NSCLC	Non–Small Cell Lung Carcinoma
OAC	Oral Anticoagulants
OAT6	Organic Anion Transporter 6
OCP	Oral Contraceptive Pills
OMCS	Oculomucocutaneous Syndrome
OR	Odds Ratio
OTC	Over-The Counter
PABA	Para-Amino Benzoic Acid
PAS	Periodic Acid Schiff
PCA	Patient-Controlled Analgesia
PCT	Porphyria Cutanea Tarda
PDC	Plasmacytoid Dendritic Cell
PDGFR-β	Platelet-Derived Growth Factor Receptors Beta
PDR	Paradoxical Drug Reactions
PF	Pemphigus Foliaceous
PGD2	Prostaglandin D2
PGP	P-Glycoprotein
PI	Protease Inhibitor
PML	Polymorphonuclear Leucocyte
PMLE	Polymorphic Light Eruption
PMN	Polymorphonuclear Neutrophils
PNGD	Palisaded Neutrophilic Granulomatous Dermatitis
PPE	Palmoplantar Erythrodysesthesia
PPL	Penicilloyl Polylysine
PPV	Positive Predictive Value
PR	Pityriasis Rosea
PS	Purpura Simplex
PUVA	Psoralen and Ultraviolet A
PV	Pemphigus Vulgaris
PvPI	Pharmacovigilance Programme of India
PZA	Pyrazinamide
QN	Quinacrine
RA	Rheumatoid Arthritis
RAAS	Renin–Angiotensin–Aldosterone System

RANTES	Regulated on Activation, Normal T Cell Expressed And Secreted
RAST	Radio Allergen Sorbent Test
RBC	Red Blood Cell
RCM	Radio Contrast Medium
RDD	Rapid Drug Desensitization
Regi-SCAR	A Multinational Collaborative Research Team For Study of Severe Cutaneous Adverse Reactions to Drugs
RFT	Renal Function Test
RSS	Red Scrotum Syndrome
RT-PCR	Reverse-Transcriptase Polymerase Chain Reaction
RUCAM	Roussel Uclaf Causality Assessment Method
SAE	Serious Adverse Event
SCAR	Severe Cutaneous Adverse Reactions
SCC	Squamous Cell Carcinoma
SCF	Stem Cell Factor
SCORTEN	Score of Toxic Epidermal Necrosis
SDRIFE	Symmetrical Drug-Related Intertriginous and Flexural Exanthema
SEDA	Side Effects of Drugs Annuals
SIADH	Syndrome of Inappropriate Antidiuretic Hormone (Secretion)
SJS	Stevens–Johnson Syndrome
SJS/TEN	Stevens–Johnson Syndrome/Toxic Epidermal Necrolysis
SLE	Systemic Lupus Erythematosus
SMO	Smoothened Homologue
sMPE	Severe Maculopapular Exanthem
SNP	Single-Nucleotide Polymorphism
SPT	Skin Prick Test
SPT/IDT	Skin Prick Test/Intradermal Test
SS	Sweet's Syndrome
SSLR	Serum Sickness Like Reaction
SSSS	Staphylococcal Scalded Skin Syndrome
STEPP	Skin Toxicity Evaluation Protocol With Panitumumab
TAILS	TNF-α Antagonist-Induced Lupus-Like Syndrome
TB	Tuberculosis
TCA	Tricyclic Antidepressants
TCR	T-Cell Receptor
TCS	Topical Corticosteroid
TDM	Therapeutic Drug Monitoring
TEN	Toxic Epidermal Necrolysis
TGF-β	Transforming Growth Factor Beta
TKI	Tyrosine Kinase Inhibitor
TLR	Toll-Like Receptor
TMP–SMX	Trimethoprim–Sulfamethoxazole
TMP-SMZ	Trimethoprim-Sulfamethoxazole
TNF	Tumor Necrosis Factor
TNF-α	Tumor Necrosis Factor Alpha
TNF-α	Tumor Necrosis Factor-α
TPMT	Thiopurine S-Methyltransferase
TPN	Total Parenteral Nutrition
TSDF	Topical Steroid Damaged Face
TSH	Thyroid-Stimulating Hormone
TST	Tuberculin Skin Test
TTP	Thrombotic Thrombocytopenic Purpura
UMC	Uppsala Monitoring Centre
UV	Ultraviolet
UV	Urticarial Vasculitis
UVB	Ultraviolet B
UVA	Ultraviolet A
UVA/UVB	Ultraviolet A/Ultraviolet B
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
VRESS	Viral Reactivation with Eosinophilia And Systemic Symptoms
VZV	Varicella Zoster Virus
WHO-UMC	World Health Organization-Uppsala Monitoring Centre

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Chapter 1

Introduction: Nosology, History and Classification of Adverse Drug Reactions

Abhay Mani Martin • Lalit Kumar Gupta

SUMMARY

Any substance that is capable of producing a therapeutic effect can also produce unwanted or adverse effects. Adverse drug reactions are a major public health burden and account for significant morbidity and mortality. All clinicians should have a basic knowledge about the terminology, classification, and mechanisms of adverse drug reactions (ADRs). This chapter briefly deals with definitions, history, and classification of adverse drug reactions that is of practical relevance to a clinician.

DEFINING ADVERSE DRUG REACTIONS

Drugs or medicaments administered for therapeutic response can produce untoward effects which have been termed adverse drug reactions (ADRs). Defining these adverse reactions has always been difficult and less than perfect. An ideal definition must take into account several factors including the type of dosing (test dose, therapeutic dose, prophylactic dose–like vaccines, diagnostic dose–like radiocontrast), nature of medications used (active principle, excipients, herbal medications), harmful or unpleasant outcomes (which ranges from transient physiologic effects to severe morbidity or mortality) and action needed (dose reduction, drug withdrawal, avoiding it's use in future). The classical World Health Organization (WHO) definition in vogue for over three decades is the most prevalent.[1] In spite of its fallacies, it is still the most widely used definition for surveillance purposes. Definitions have also been proposed by Laurence and Carpenter[2] and by Edwards and Aronson.[3] The three definitions are compared in Table 1.1.

Table 1.1: Definitions of adverse drug reactions and their comparison

Definition	Author	Remarks
A response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function.	WHO definition[1]	Term "noxious" is not accurately defined. Reactions can occur at doses lesser than "normally used in man" e.g. test doses. Does not account for errors as cause of ADRs. Prone to subjectivity in surveillance.
A harmful or significantly unpleasant effect caused by a drug at doses intended for therapeutic effect (or prophylaxis or diagnosis) which warrants reduction of dose or withdrawal of the drug and/or foretells hazard for future administration.	Laurence and Carpenter[2]	Does not account for medical errors as cause of ADRs.
An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.	Edwards and Aronson[3]	Uses the term "medicinal product" in an attempt to include reactions arising out of herbal medications and inactive formulations like excipients.

ADRs - adverse drug reactions; WHO - World Health Organization.

A good standard definition is an essential prerequisite for proper documentation, for epidemiologic studies, and for the clinician to report ADRs to appropriate authorities. The definition needs to be unambiguous so as to avoid confusion to the clinician and the epidemiologist. This ensures proper registry entries based on an accurate definition. This "perfect" definition of ADR remains elusive. An ADR includes all drug related adverse events associated with drug administration irrespective of its mechanism.

How Does a "Rash" Become Classified as an ADR?

At the bedside, the process of recognizing a rash as an ADR involves systematic, stepwise logical sequencing of events and evidences along with clinical judgment based on experience. The experienced clinician can pick up subtle findings as well as sift out irrelevant details. A stepwise approach to this is alluded to in Chapter 7. This, combined with attribution of causality based on reported findings in literature, helps label a rash as an ADR.

A new drug introduced into the market undergoes toxicological and pharmacological tests in animals, followed by clinical trials in humans. This is then followed by postmarketing surveillance for ADRs. This systematic process does not usually encompass more than 4000 patients before approval. Therefore, drug reactions that occur in less than 1 in 1000 patients are difficult to detect.[1] Further premarketing trials do not include special populations like pregnant and lactating women. It also does not account for multiple comorbidities and real life situations wherein the drug may be administered after approval. Drugs may also be used for off label indications. This underscores the importance of postmarketing surveillance. Such adverse events that get reported in postmarketing trials or when in use by the general population become crucial in identifying reactions as it involves larger populations and includes multiple real-life situations. Hence ADR reporting is a crucial exercise that enhances the database of such reactions to a particular drug. This database becomes a useful resource and reference guide for judicious use of medications.

HISTORY OF ADR

The earliest reference to adverse reactions to medications can be dated to 1881 when the German toxicologist, Louis Lewin, published the book, *Die Nebenwirkungen der Arzneimittel*, which was devoted entirely to adverse effects of drugs. Three editions were subsequently published in 1893, 1899, and 1909. In 1883, Dr. J.J. Mulheron, Professor of the Principles of Medicine, Materia Medica, and Therapeutics of Michigan College of Medicine translated this book to English and published it as the "second edition" titled *The Untoward Effects of Drugs*. In 1905, *The British Medical Journal* published a series of articles titled "The Composition of Secret Remedies" which dealt with drugs used to treat epilepsy, headache, kidney, and other diseases. In 1915, Otto Seifert, wrote the book titled *Die Nebenwirkungen der modernen Arzneimittel,* a 278-page-volume textbook on adverse effects of drugs. The problems encountered with Salvarsan led to establishment, in United Kingdom, of the Therapeutic Substances Act of 1925 which was later superseded by the Medicines Act of 1968. In 1951, Leopold Meyler published a booklet in Dutch, reporting the adverse effects of drugs. Its English translation *Side Effects of Drugs* was published in 1952, which was subsequently published as volumes, annually. Hence its name was changed to Side Effects of Drugs Annuals (SEDA). They are published in volumes rather than editions and currently run to 33 volumes.

The current modern scheme of recognizing ADRs and its reporting has been spearheaded internationally by the WHO, through its Uppsala monitoring centre (UMC) at Uppsala , Sweden, established in 1971. It started with 10 member countries but several countries have joined in. European Union countries have a strong reporting system and some countries even have a mandatory reporting system too. This has contributed to a robust surveillance system which has resulted in unearthing hitherto undiscovered ADRs to drugs. Classic examples include the identification of ADRs to rofecoxib (cardiovascular disease), astemizole (interactions with grapefruit juice), and cisapride (QT prolongation). Table 1.2 shows some drugs that have been removed from the market or whose use has been restricted.

Table 1.2: List of some drugs withdrawn from the market/restricted on account of their systemic adverse effects

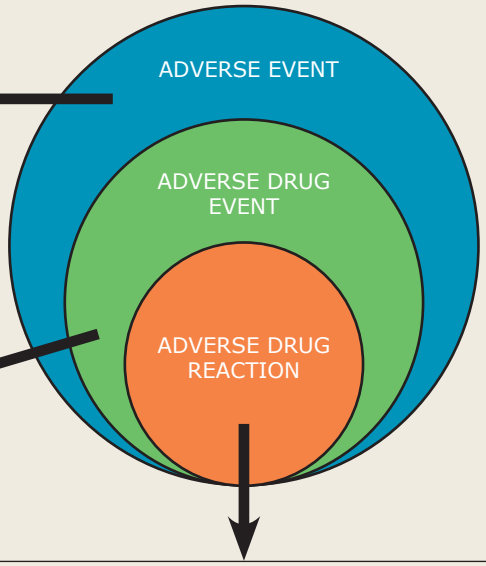
Drug	System affected	Action
Cisapride, Terfenadine	Cardiac arrhythmias/QT prolongation	Withdrawn from market
Thalidomide	Congenital anomalies	Withdrawn from market
Rofecoxib	Hepatic derangement	Withdrawn from market
Rosiglitazone	Cardiac involvement	Withdrawn from market
Chloramphenicol	Blood dyscrasias	Use restricted
Aspirin	Reye's syndrome (in children)	Use restricted

CASE SCENARIO
Sixty-five-year-old gentleman had a low back ache for which he was prescribed Ibuprofen. He was admitted with a generalized itchy maculopapular rash, skin tenderness, and erosions on the lips. On the same day he developed a hematoma at the site of iv cannulation for fluid replacement. On day 3, he had pain in the epigastric region which was diagnosed as gastritis and treated with pantoprazole. He developed an acute stroke of the right middle cerebral artery (MCA) territory on the same day. He was managed with steroids for the rash and antiplatelets for the thrombotic stroke.

ADVERSE EVENT
- Stroke occurred after drug administration but is unrelated to the drug (Ibuprofen) and is independent of it.
- Causal relationship with drug does not exist.
- Need not occur in normal doses of the drug.
- No literature support to suggest that the event (stroke) is related to the drug, Ibuprofen.
- Thus the stroke is an adverse event unrelated to the drug ibuprofen.
- Hematoma is also an adverse event on the above lines.

ADVERSE DRUG EVENT
- Gastritis occurred after drug administration but may be unrelated to the drug (like preexisting illness).
- Causal relationship with drug need not exist
- It is not related to normal dose of the drug; can occur with higher doses (ibuprofen causes acidity).
- Literature support exists to suggest that the event(acidity) is related to the drug at higher doses.

Thus acidity is an adverse drug event as it is attributable to a higher dose of the drug. But not normal doses.



ADVERSE DRUG REACTION
- Causal relationship with drug is necessary (Ibuprofen and SJS).
- Occurs with normal doses of the drug.
- Literature support exists to suggest that the event is related to the drug.
- Maculopapular rash and erosions of lips are features suggestive of early SJS and Ibuprofen is known to cause this ADR.
- Hence SJS is an adverse drug reaction to Ibuprofen.

Fig. 1.1: Understanding the difference in terminologies.

In India, ADR reporting is in its infancy. The program has been spearheaded by the Pharmacovigilance Programme of India (PvPI). Health care professionals (HCPs) report ADR to nearby ADR Monitoring Centres (AMCs) under PvPI. This information is then collected and collated by the Indian Pharmacopoeia Commission (IPC), National Coordination Centre (NCC), Ghaziabad.

Terminology/Nosology

There is much confusion regarding the use of terminology with reference to the untoward effects of drugs. Terms like adverse reaction, adverse event, toxic effect, and side effect are used synonymously by patients and physicians alike. Although it is absolutely essential that these terminologies are clarified when conducting clinical trials or publishing, it would be wise for the physician to use these terms appropriately in clinical parlance too. Table 1.3 provides a useful guide to the commonly used terminologies.[4] Figures 1.1 and 1.2 illustrate the basic difference between adverse event and adverse drug reaction.

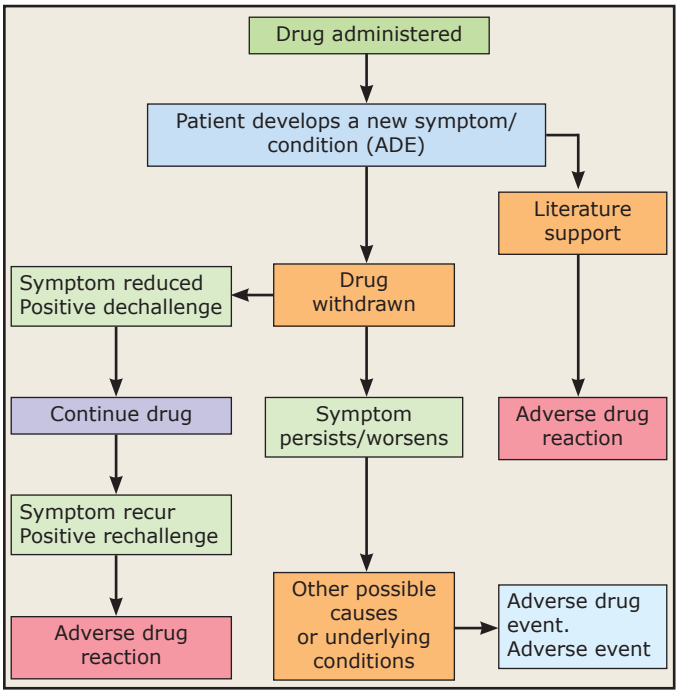


Fig. 1.2: How to recognise an event as adverse event (AE) or adverse drug reaction (ADR).

Table 1.3: Some commonly used terms in drug reactions

Terminology	Interpretation	Explanation/Examples
Adverse effect vs Adverse reaction	What the drug does to the body	These terms have a subtle difference.
	How the body reacts to the drug	The changes a drug may induce at the enzymatic, cellular, or organ level is called an *adverse effect* (e.g. elevation of blood pressure) whereas the body's reaction to the drug administered is called an *adverse reaction* (e.g. rash, gastritis, hepatitis).
Toxic effect	It is an exaggeration of the desired therapeutic effect that is unwanted and is *always dose related.*	Headache due to calcium antagonist—both headache and reduction of hypertension are due to the same effect namely vasodilatation but the former is a toxic effect.
Side effect	A therapeutic effect that is *not dose related.* It may be unwanted or beneficial.	1. A patient developing drowsiness when given an antihistamine for an itch is an unwanted effect whereas relief of rhinitis (antihistaminic action) or irritable bowel (anticholinergic action) is a beneficial effect. 2. A patient on beta blocker for hypertension also gets relief of angina (beneficial effect) but may develop worsening of asthma (unwanted effect).
Adverse event	An adverse drug reaction is an adverse outcome that *can be attributed*, with some degree of probability, to an action of a drug. An adverse event is an adverse outcome that occurs while a patient is taking a drug, or at some time afterward but *may or may not be attributable* to it.	All adverse reactions are adverse events but not vice versa The key difference between the two terms is in "attributability" The adverse reaction must be attributed to the particular drug the patient is taking. A Patient developing acidity while on NSAID is attributable to the drug and hence it is an *adverse reaction.* However, if the same patient develops blurred vision while on the NSAID, it is an *adverse event* as the symptoms may or may or may not be attributable to the drug though the event did occur at the point in time the drug was taken.

NSAID - nonsteroidal anti-inflammatory drugs.

CLASSIFICATION OF ADRs

There are several classifications of ADRs in vogue. However, the classification by Rawlins and Thompson[5] is the most commonly used. It has two major subtypes:

Type A reactions (pharmacologic reactions) which are predictable and are due to the pharmacologic property of the drug. They are more common, dose dependent, and usually mild.

Type B reactions (hypersensitivity reactions) are hard to predict and "occur" in predisposed individuals. These are relatively uncommon, bear no simple relationship with dose and are more severe.

Table 1.4 presents a more comprehensive and practical scheme of classification that encompasses major types of ADRs with their mechanisms and examples.

CONCLUSION

ADRs, despite being an important cause of iatrogenic morbidity and mortality in the medical field across the globe, lack a uniformly accepted definition and classification. An ideal scheme to define, classify, and elucidate the mechanisms of ADRs is still elusive. Adopting common definitions, terminology, and classification is important to achieve the goal of safe drug administration and understand the etiopathogenetic mechanisms. It will also have a bearing on the effective management of the patients. Knowledge of these definitions and classifications ensure uniformity in reporting and in surveillance.

Table 1.4: A comprehensive classification of ADR

Type	Mechanism	Subtypes	Examples
Type A (Augmented) Predictable Dose dependent	Due to pharmaco toxicologic effects of drugs	a. Pharmacologic action	Sedation with antihistamines
		b. Medication errors—overdosage or under dosage	
		c. Drug interactions—food, other drugs and illnesses	Cyclosporine and grape fruit juice interaction
		d. Impaired metabolism or excretion(e.g. hepatic or renal disease)	Increased drug concentration in renal disease
		e. Effects unrelated to the drug	
Type B (Bizzare) Unpredictable and non-dose-dependent	Nonspecific mechanisms	a. Defective or absent enzymes	G6PD deficiency in dapsone-induced hemolysis
		b. Cytokine imbalance	Cytokine release syndrome with monoclonal antibodies (anaphylaxis to NSAIDS)
		c. Inflammatory mediator imbalance	Bradykinin-mediated angioedema in ACE inhibitor use
		d. Nonspecific mast cell degranulation	Codeine and morphine-induced urticaria. Radiocontrast and neuromuscular blocking agents induced anaphylaxis reactions.
	Specific immune reactions	Type I: IgE mediated	Anaphylaxis to NSAIDS
		Type II: IgG-mediated cytotoxicity	Drug-induced pemphigus/pemphigoid
		Type III: Immune complex deposition	Drug induced lupus erythematosus/ vasculitis
		Type IV: T-cell mediated:	
		IV a. Monocytic inflammation	Bullous exanthems, SDRIFE
		IV b. Eosinophilic inflammation	Maculopapular rash, DRESS
		IV c. Cytotoxic T cells	FDE, SJS/TEN
		IV d. Neutrophilic inflammation	Pustular exanthema/AGEP

Source: Adapted and modified from Hausmann, et al.[6]

ACE - angiotensin converting enzyme; NSAIDs - nonsteroidal anti-inflammatory drugs; SDRIFE - symmetrical drug related intertriginous and flexural eruption; DRESS - drug reaction with eosinophilia and systemic symptoms; FDE - fixed drug eruption; SJS - Stevens-Johnson syndrome; TEN - toxic epidermal necrolysis; AGEP - acute generalized exanthematous pustulosis.

LEARNING ESSENTIALS

- ADRs are frequently encountered in clinical practice.
- Recognizing ADRs needs clinical expertise and standardized definitions. Attempts at bringing out a standard definition of ADR have been elusive thus far; WHO definition of ADR is still the most widely used.
- The nosology used in relation to ADRs can at times be confusing. This chapter has attempted to clarify concepts in relation to the usage of appropriate terminologies.
- Classification of ADR helps to identify the etiopathogenesis of the drug reactions. A knowledge of classifications helps to sort reactions into categories and aids in pharmacovigilance.

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Chapter 2

Epidemiology of Cutaneous Adverse Drug Reactions

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SUMMARY

Adverse reactions to drugs are common in clinical practice and reactions affecting skin form a sizeable percentage of these reactions. Epidemiologic studies, with respect to drug reactions are lacking as there are very few well-designed studies. The scenario is dismal in the Indian context as adverse drug (ADRs) are grossly under reported. Among the reported cutaneous adverse drug reactions (CADRs), morbilliform drug rash, and fixed drug eruptions are the commonest morphologic patterns noted. Antimicrobials, nonsteroidal anti-inflammatory drugs (NSAIDs), and anticonvulsants are the leading classes of drugs causing CADRs. With the introduction of newer drugs into the market, newer reactions are being encountered and increased vigilance and reporting is needed. This chapter summarizes the epidemiologic patterns noted in various studies across the world including some from the Indian perspective.

INTRODUCTION

Cutaneous adverse drug reactions (CADRs) are common in clinical practice and need to be recognized early for prompt drug withdrawal and early intervention. It has been estimated in one study that 14% of adverse drug reactions in hospital care are cutaneous or allergic in nature.[1] Epidemiologic studies are a useful aid in recognizing morphologic patterns of drugs, linking CADRs to the classes of drugs, identifying and reporting unusual reactions to commonly used drugs, and reporting of ADRs to newer therapeutic agents. While serious cutaneous ADRs [severe cutaneous adverse reaction (SCAR)] are often reported in epidemiologic studies and case series, milder reactions go unreported.

Reporting of ADRs, especially in India, have inherent fallacies and limitations. Most studies are hospital based and are done in an inpatient setting. Outpatient studies are few, and if recognized, are not reported as per standard guidelines. Hospital-based studies tend to be biased in their reporting toward serious adverse events and they do not reflect the load of adverse reactions in the general population. Further, less serious reactions go unreported as they may self-limit or are likely to be self-treated by the patient. Reactions of a moderate nature are reported to and treated by a nondermatologist (primary-care physician, pediatrician, etc.). Cutaneous ADRs that reach the dermatologist are those which are beyond the scope of the primary physician or are of a serious nature (e.g. SCAR) or life threatening (e.g. toxic epidermal necrolysis, erythroderma and anaphylaxis). The dermatologist must be motivated enough to report the same. Data also arise from cross-sectional studies/case series. They are most often reported from academic institutions or by well meaning, self-motivated clinicians in clinical practice.

As newer drugs emerge into the market, newer adverse reactions are being reported. It is noteworthy that of the newer drugs in the market, more than half the drugs have serious side effects.[2] Reporting of adverse reactions is crucial with new molecular entities (NMEs), new therapeutic biologics under biologics license applications (BLAs), and some orphan drugs as they are a predictor of adverse reactions when used in the clinical setting.

Epidemiologic studies on ADRs may be done by pharmaceutical manufacturers (as clinical trials—pre- and postmarketing), may be reported by pharmacovigilance groups (self-reported or mandatory reporting), or may be done as part of academic research studies. All these data accrue

to help gain valuable insight into patterns of drug reactions.

Faulty reporting may occur due to over reporting as well as under reporting of drug reactions. Further, the similarity in presentation of drug reactions [especially maculopapular exanthema, erythema multiforme, and Stevens–Johnson syndrome (SJS)] and viral or bacterial eruptions [measles, herpes-associated erythema multiforme (EM), scarlet fever, etc.] makes it difficult to characterize the rash as drug or infective etiology.

INCIDENCE OF CADR IN DIFFERENT SETTINGS OF CLINICAL CARE

The incidence of CADRs is influenced by the care setting. Outpatient studies are few in number. Inpatient studies have a higher incidence of CADRs probably due to greater reporting of SCAR. Among hospitalized inpatients, adverse drug reactions constituted 19% of all hospital-related adverse events (this includes mishaps, negligence, and other medical errors), according to a study by Leape et al.[1] In a study by Bigby et al. on 15,438 consecutive inpatients, the overall cutaneous ADR rate was 2.2%.[3] It has been estimated that 5% of all hospital admissions are due to ADR and that 5% of all hospitalized patients will experience an ADR during their hospital stay and that ADRs cause 197,000 deaths throughout the European Union (EU). Of these ADRs, 70% had cutaneous ADRs.[4]

International Studies

A study from France done in 2003 analyzed ADRs from systemic drugs in a specific hospital over 6 months (n = 48 inpatients) and identified the prevalence rate to be 3.6% per 1000 hospitalized patients.[5] Another study from Mexico over 10 months reported a prevalence of 7 per 1000 inpatients (35/4765 inpatients).[6] In South Korea where electronic reporting of CADRs is mandatory, 2682 cases of ADRs were identified among 55,432 admissions over 7 months. The incidence was estimated at 1.8 per 1000 admissions.[8]

A review of recent observational studies (January 1, 2000 to September 3, 2014) on the epidemiology of ADRs in Europe was published by Bouvy et al.[7] The study included those who were hospitalized due to ADRs, those who developed ADRs while they were hospitalized, and those in the outpatient setting; 3.5% of patients were hospitalized due to ADRs (based on 22 studies) and 10.1% experienced ADRs during hospitalization (based on 13 studies). In the outpatient setting (in the five studies conducted), ADR rates varied from 0.4%–7.8%.

Indian Studies

Indian studies have reported a higher incidence rate of 2%–5% of the hospital admitted patients.[9-13] Patel et al. in their systematic review of 3671 cases reported the incidence of CADRs as 82.59/1000 and 8.72/1000 in inpatient and outpatient settings, respectively.[12] In an earlier study by Chatterjee et al., the incidence of CADRs was found to be 2.6% (i.e. 26/1000) in a dermatology outpatient setting.[13] This highlights that incidence of reporting varies widely and bias confounds true incidence of CADRs in hospital-based studies.

Demographic Distribution of CADRs

CADRs appear to be most common in second and third decades of life. The study by Patel et al. noted that the distribution of the patients was highest in the 21–39 age group, constituting 54.42% of patients (age groups 0–20, 21–39, 40–60, and >60 years were 18.84%, 54.42%, 18.78%, and 7.96%, respectively).[12] Similar observations have been echoed by other Indian studies.[11,14-17]

Some studies point to a male predilection whereas others suggest a female preponderance. Patel et al. reported male to female ratio as 1:0.9.[12] A bias due to preponderant male or female outpatient/inpatient attendance needs to be accounted for.

CADR AND MORPHOLOGIC PATTERNS

Among the CADRs, maculopapular rash was the most common pattern in a review of Indian studies done by Patel et al.,[12] Saha et al.[15] (Eastern India), Nandha et al.[16] (North India), Pudukadan et al.[11] (South India), and Hiware et al.[17] (Western India). However, the series by Sharma et al.[14] (Jammu) reported fixed drug eruption (FDE) as the most common CADR. Urticaria, acneiform eruptions, erythema multiforme, SJS-toxic epidermal necrolysis (SJS-TEN), phototoxic drug reaction, and exfoliative dermatitis were other commonly reported CADRs in various studies. The patterns of presentation in the various Indian studies are represented in Table 2.1.

Differentiating viral exanthems from maculopapular CADR is challenging and this fact may account for variations in the frequency reported. Also, studies have reported different frequencies for different CADRs. This in part can be explained by study designs (inpatients only, outpatients only, or both), strength of outpatient department and number of beds available in a particular hospital, and lack of definitive diagnostic modalities. SCARs are CADRs that could be severe and life threatening and

Table 2.1: Various Indian studies on epidemiological aspect of cutaneous adverse drug reactions

Author	No. of patients	Study design	Most common age group	Male: female ratio	Common CADR	Common culprit drugs
Sharma et al, 2015	150	Prospective observational study of 13 months duration	21–30 years (30.6%) 31–40 years (26%)	1.21:1	• FDE (33.3%) • Urticaria (17.3%) • Maculopapular rash (13.3%) • Acneiform eruptions (11.3%) • Erythema multiforme (10%)	• Antimicrobials (40%) • NSAIDs (35.3%), • Steroids (14.67%) • Anticonvulsants (5.33)
Patel et al, 2014	3671	Systematic review of Indian literature published between January 95 to April 2013	21-39 years (54.42%)	1:0.9	• Maculopapular rash (32.39%) • FDE (20.13%) • Urticaria (17.49%) • SCARs (8.17%)	• Antimicrobials (45.46%) • NSAIDs (20.87%) • Antiepileptics (14.57%) • Sulfa drugs (13.32%), β-lactams (8.96%), Carbamazepine (6.65%), Phenytoin (6.46%), Fluoroquinolones (5.12%), Ibuprofen (4.71%), Nitroimidazole (4.17%), Antituberculars (2.81%)
Hiware et al, 2013	872	Prospective observational study of 48 months duration	21- 30 years (40.48%) 31-40 years (21.1%)	1.79:1	• Maculopapular rash (37.73%) • FDE (17.2%) • Urticaria (14.56%) • Pruritus (9.06 %) • Flaring of tinea (Tinea incognito) (6.54%) • Acneiform eruptions (5.62%)	• Antimicrobials (55.5%). • NSAIDs (18.56%) • Cotrimoxazole (20.41%) topical betamethasone (9.06%), Ibuprofen (7.91%), Ampicillin (6.54%), Diclofenac sodium (4.7%), Iron dextran (3.44%), ciprofloxacin (3.33%), isoniazid (3.21%), chloroquine (2.41%), and metronidazole (2.06%)
Saha et al, 2012	53	Prospective observational study of 12 months duration	16-35 years (52.80%)	1.04:1	• Morbilliform eruption (30.18%) • FDE (24.52%) • SJS-TEN and overlap of these two (24.50%) • Exfoliative dermatitis (7.54%) • Urticaria (5.6%) • Phototoxic drug reaction (3.8%)	• Sulfonamides and allied drugs (17.00%) • Fixed dose combinations of fluoroquinolones with nitroimidazoles (11.30%) • Analgesics (11.30%) • Antiepileptics (11.30%), • β-lactam antibiotics (9.40%), • Fluoroquinolones alone (7.50%), • Allopurinol (7.50%) • Azithromycin (5.70%)
Nandha et al, 2011	91	Prospective observational study of 6 months duration	21–30 years (25.27%), 31–40 years (23.07%)	0.94:1	• Maculopapular rash (42.85%) • FDE (20.87%) • Urticaria (12.08%) • Photosensitivity (4.39%).	• Antimicrobials (48.30%), • NSAIDs (21.90%) • Anti-epileptics (13.20%)
Sushma et al, 2005	404	Retrospective observational study of 108 months duration	21-40 years	1.09:1	• Maculopapular rash (42.7%) • Stevens-Johnson syndrome (SJS) (19.5%) • FDE (11.4%)	• Antibiotics (45%), • Antiepileptics (19%) • NSAIDs (19%)
Pudukadan et al, 2004	90	Observational study between 2001-2003	20-39 years (52.22%)	0.87:1	• FDE (31.1%) • Maculopapular rash (12.2%)	• Antimicrobials (58.88%) • Antiepileptics (15.55%) • NSAIDs (15.55%) • Co-trimoxazole (22.2%), Dapsone (17.8%), Phenytoin (7.8%), Carbamazepine (7.8%).

include SJS, TEN, drug hypersensitivity reactions (DHRs) or drug reaction with eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS), and acute generalized exanthematous pustulosis (AGEP). Fortunately, SCARs are uncommon and are believed to constitute 5%–14% of CADRs.[18] The review by Patel et al. stated that it contributed 8.17% of CADRs of which SJS/TEN appears to be commonest and contributed 6.84% of CADRs.[12] Devi et al. have documented female preponderance in their study on 37 SCARs patients. Majority of patients were in 21–40 years age group (just like CADRs).[19] Sasidharanpillai et al. have found male preponderance (except for DRESS) and 40–60 years age group as major affected age group.[20]

CADR AND CULPRIT DRUGS: CAUSALITY

Attribution of a drug to the suspected drug reaction is difficult as there are no uniform criteria laid out for diagnosing the same. Causality assessment scales (Naranjo's causality assessment scale[21] and World Health Organization-Uppsala Monitoring centre (WHO-UMC) standardized case causality assessment criteria[22]) differ in their criteria and hence studies reporting ADRs show disparity. Though drug rechallenge is an essential criteria in both the scales—and it is the one reliable way to establish a diagnosis, risk–benefit assessment, and ethical constraints limit its utility as a diagnostic modality, as it may evoke a life-threatening or seriously disabling reaction. The issue of diagnosis of CADRs is further complicated by the fact that skin rashes that occur in bacterial or viral infections can mimic the rash of ADRs, and hence, establishing the causality in suspected CADRs with antimicrobial agents is often problematic.

The major culprit drugs that were identified for CADRs were antimicrobials (45.46%), NSAIDs (20.87%), antiepileptics (14.57%), and corticosteroids (3.87%).[12] Other studies too have observed similar trends and their findings have been summarized in Table 2.1. Antimicrobials and NSAIDs are one of the most frequently prescribed medicines. Further, self-medication with these drugs is rampant, especially in India, due to easy availability of drugs, over the counter. This in part may explain the higher incidence of CADRs to these drugs.

Antibiotic prescribing patterns have changed and there has been as shift toward third-generation cephalosporins, newer quinolones, and macrolides. An increased awareness of sulfa-related drug reactions and the high risk of SJS-TEN in patients has also contributed to a decrease in ADRs to sulfas and quinolones (authors' personal observations).

Another fact that also has to be taken into account is the variation in the medication prescribed in different setups. Centers that cater to specific disease populations like HIV or cancer institutes are likely to encounter drug reactions related to that specific group of drugs. Hence prevalence/incidence rates from such centers tend to be skewed to disease-specific drugs.

Fixed dose combinations of quinolones and nitroimidazoles are also a common cause for CADRs.[14] Antiepileptics like carbamazepine and phenytoin were the common agents implicated in SCARs. For fluoroquinolones, ratio of severe to non severe CADRs was less than 1:10.[7] Similar observations were made in studies by Devi et al. and Sasidharanpillai et al.[14,15] Sasidharanpillai et al. have reported antiepileptics as a common cause for SCARs.[15]

CADR AND LATENT PERIOD

The latent period between drug intake and onset of symptoms vary depending on the reaction pattern and the offending drug and this has been documented as <1 hour to 172 days[12] Urticaria and angioedema appeared earliest within minutes. However, late appearance of urticaria up to 4 weeks too has been reported. Most CADRs presented with a latent period of 1 day to 4–8 weeks. Late presenting CADRs include lichenoid reactions (5 days), vasculitis (7 days), acneiform eruptions (10 days to 4 weeks), and hyperpigmentation (4 weeks)[12] Nandha et al. reported latency ranging from less than 2 days to 30 days, with most patients presenting between 2 and 14 days.[15] SCARs with an exception of DRESS presented mostly within 1–4 weeks of drug intake, with TEN (mean 17.7 days) presenting bit earlier than SJS (mean 27.5 days). However, the difference in latency between SJS and TEN was not statistically significant and a larger study is needed to confirm or refute this observation. DRESS is a late presenting SCAR, latency varying from 21 to 90 days with an average of 37 days.[23]

Drugs-related variation in latent period too is notable. Fixed dose combinations of fluoroquinolones and nitroimidazole are one of the most common causes of FDE and usually lead to early CADRs (latency 1 day, median). On the other hand, allopurinol-related CADRs present late (mean 16.3 days, median 18 days).[18] A proper understanding of latent period is very important in establishing causality

since without proper knowledge regarding long latent period, a drug may be classified as unrelated in terms of causality.

CADR AND THEIR SEVERITY

Severity of CADR is judged by Hartwig's severity scale[24] and all SCARs that belong to severity level 4 or more require admission. It has been documented that 11.39% of CADRs necessitated hospitalization and SCARs can also have a severity of level 7 (death of patient).[12] The same review of Indian studies by Patel et al. noted that the commonly observed complications were altered liver functions (3.90%), septicemia (2.54%), and acute renal failure 2.54%. An overall mortality of CADRs, SJS/TEN, exfoliative dermatitis, erythema multiforme, and maculopapular rashes was 1.71%, 16.39%, 3.57%, 0.13%, and 0.45%, respectively.[12] The mortality rate was significantly higher in SJS/TEN compared with overall CADRs, erythema multiforme, and maculopapular rashes.[7] TEN has been found to be associated with mortality rate 25%–30%.[18,20] Ocular involvement is common in SJS/TEN and may lead to long-term morbidity (level 6 severity, i.e. permanent harm to patient).[19,20]

CONCLUSION

Epidemiologic studies are vital in identifying key etiopathogenetic factors and clinical patterns of drug reactions. There is paucity of studies done world over and more so in the Indian context. Epidemiologic studies provide vital information on trends of drug reactions (patterns, causality, and severity) as well as help in capturing newer drug reactions.

The gap in knowledge needs to filled by a concerted effort by all the stakeholders in the process—namely dermatologists, physicians, pharmacists, pharmaceutical agencies, and reporting authorities. Patients can also play a role in this by actively reporting such adverse drug reactions and subjecting themselves to a systematic evaluation. The role of pharmacovigilance as per protocols prescribed by Pharmacovigilance Programme of India (PVPI) and WHO-UMC, is vital in the proper reporting of drug reactions.

LEARNING ESSENTIALS

- Epidemiologic studies on CADRs are few and especially so from the Indian subcontinent.
- CADRs are common in the second and third decades of life though no gender predilection was identified in studies.
- Maculopapular rash, fixed drug eruption, urticaria, and SJS/TEN are the commonly encountered CADR in its decreasing order of incidence.
- Causality is difficult to establish definitively in CADR and rechallenge is unethical, especially in SCARs. Data based on current scoring systems suggest that antimicrobials, NSAIDs, and antiepileptics are the major culprit.
- The latent period of CADR can range from <1 hour to 172 days and depends on the culprit drug. Urticaria may occur in minutes whereas DRESS may take several weeks.
- SCAR comprising of SJS/TEN, exfoliative dermatitis are at times fatal and also can cause systemic complications.

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Chapter

3

Immunopathogenesis of Drug Reactions

Brijesh Nair

SUMMARY

Approximately 20% of cutaneous adverse drug reactions are immune-mediated adverse drug reactions (IM-CADR). The IM-CADR can be classified based on the lines of Gell and Coombs hypersensitivity reactions from type I to type IV. The role of human leukocyte antigen (HLA) genes and the role of alleles in predicting drug reactions are very important. The T cell receptor clonotype, in addition to HLA, decides the nature of resulting ADR. The various immunological concepts including hapten/prohapten concept, pi concept, and altered peptide repertoire concept explain the multifarious presentations of IM-ADR. The role of viruses as the initiator and propagator of IM-ADR is of paramount importance and the new model of heterologous immunity best explains the role of viruses, but needs further research to validate the proof of concept.

INTRODUCTION

Cutaneous adverse drug reactions (CADRs) are one of the most common causes of morbidity and mortality in dermatology. Around 10–20% of CADRs are immune-mediated CADR (IM-CADR). These reactions stem from specific off-target drug activity and include the IM- adverse drug reactions (IM-ADRs), as well as off-target pharmacologic drug effects, such as those seen in patients with non-IgE-mediated mast cell activation syndrome. Off-target induction of an immune system-mediated reaction is an adverse immunological reaction and is known as a hypersensitivity reaction.[1] IM-ADRs encompass a number of phenotypically distinct clinical diagnoses that comprise both B-cell-mediated (antibody-mediated, Gell–Coombs types I–III) and purely T-cell-mediated (Gell–Coombs type IV) reactions. Among these classes, the types that are not of much importance to CADR are type II (mostly hematological toxicities such as immune thrombocytopenias and hemolytic anemias) and type III hypersensitivity (immune complex–mediated disease). We shall mostly be confining to the most relevant types, type I (IgE-mediated CADR) and type IV (delayed-type hypersensitivity).The aim of this chapter is to sensitize the practicing dermatologists regarding the broad tenets of immunopathogenesis of IM-CADR.

TYPE I HYPERSENSITIVITY

IgE-mediated drug reactions including urticaria, angioedema, and anaphylaxis are type I hypersensitivity reactions and involve drug-specific IgE bound to the high-affinity IgE receptor (FcεR1) on the surface of mast cells and basophils. IgE binding to a multivalent allergen (drug) induces receptor aggregation and leads to cellular activation, followed by degranulation and release of inflammatory mediators including histamine. The mediators are divided into three groups: (1) those that are performed in granules; (2) newly synthesized lipid mediators; and (3) cytokines and chemokines. In the skin, the release of histamine, leukotriene C4 (LTC4), prostaglandin D2 (PGD2), and proteases contribute to early vasodilatation and increased vascular permeability, which induces redness and edema associated with wheal and flare. LTB4 and cytokine release induces an eosinophil [interleukin 5 (IL-5)] and neutrophil [IL-8 and tumor necrosis factor α (TNF-α)] influx that contributes toward a late phase reaction, which can develop 5–6 hours after the onset of the anaphylaxis. The regulation of B cell IgE production is dependent on antigen-specific Th2 signaling in the lymph node. The reported associations between type I hypersensitivities and human leukocyte antigen (HLA) alleles are weak. STAT6 polymorphisms have been reported to predispose to penicillin

allergy. Polymorphisms in FcεR1 are associated with non-steroidal anti-inflammatory drug (NSAID) hypersensitivity. Although mostly of weak predictive value, the association between penicillin allergy and IL-4Rα polymorphisms has shown to be the most replicated of the genetic associations. Reactions mediated by type I mechanisms can begin within seconds or minutes of exposure to the relevant drug.[2]

TYPE II (IgG-MEDIATED CYTOTOXICITY), TYPE III HYPERSENSITIVITY (IMMUNE COMPLEX DEPOSITION)

These two Gell–Coombs hypersensitivity patterns have limited relevance to CADRs and hence will not be elaborately discussed. Type II reactions are based on immunoglobulin-mediated cytotoxic mechanisms, accounting mainly for blood cell dyscrasias; type II reactions are based on IgG molecules predominantly directed against erythrocytes, leukocytes, platelets, and probably also hematopoietic precursor cells in the bone marrow and subsequent complement-dependent cytotoxicity of these cells. The antibody (and complement)-coated cells will be sequestrated to the reticuloendothelial system in the liver and spleen by Fc or complement receptor binding or, more rarely, intravascular destruction may occur by complement-mediated lysis.[3]

On the other hand, type III reactions are immune complex mediated (e.g. vasculitis). Type III reactions involve small circulating immune complexes sticking to the endothelium of cutaneous venules, fixing complement, and attracting neutrophils. This damages the endothelium such that red cells extravasate into the tissues resulting in hemorrhage/purpura -the clinical and microscopic picture of vasculitis.[4]

TYPE IV HYPERSENSITIVITY (T-CELL-MEDIATED, DELAYED DRUG HYPERSENSITIVITY REACTIONS)

Type IV reactions are mediated by T lymphocytes and called "delayed type" because they characteristically develop over 24–48 hours following challenge with the causative agent. Type IV reactions have been further subclassified into types IVa–d. The clinically relevant T-cell-mediated drug reactions have been classified into delayed exanthema without systemic symptoms (maculopapular eruption), contact dermatitis, drug-induced hypersensitivity syndrome (DIHS)/drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), fixed drug eruption (FDE), and single organ involvement pathologies, such as drug-induced liver injury (DILI) and pancreatitis (e.g. azathioprine induced).[4]

Type IV delayed hypersensitivity reactions causing CADR have been subdivided according to production of distinct cytokines: Th1 for type IVa, Th2 for type IVb, and cytotoxic T cells for type IVc (Table 3.1). If T cell function leads to monocyte/macrophage activation, it is called a type IVa reaction.[5] This immune response probably best correlates to a Th1 reaction leading to a delayed-type reaction, as in a tuberculin skin test. It is distinct from a predominantly eosinophilic inflammation, which is due to a vigorous Th2 response with high IL-5 production (type IVb). T cell mediated cytotoxicity (by CD4 and $CD8^+$ T cells) is an important function in various immune reactions and in particular for most drug-induced exanthems (type IVc reactions); and the T-cell-regulated, sterile, neutrophil-rich pustule formation can be traced to high IL-8 production by T cells, which can be termed a type IVd reaction. An overlap of these immune reactions is common in clinical manifestations of drug allergies, but frequently one type is dominant.[6] The hypersensitivity types associated with various IM-ADRs are given in Table 3.1.

HUMAN LEUKOCYTE ANTIGEN

The HLA gene complex resides on chromosome 6p21. There are three classes of major histocompatibility complex (MHC) that regulate various aspects of the immune activation process.[7] They are as follows:

- **MHC class I (A, B and C):** It presents intracellular peptides and brings fragments of the virus to the surface of the cell. Foreign antigens presented by MHC class I attract $CD8^+$or cytotoxic T cells.
- **HLAs corresponding to MHC class II (DP, DM, DOA, DOB, DQ, and DR):** These present extracellular antigens to $CD4^+$ T helper cells, which in turn stimulate B cells to produce antibodies. MHC class II molecules present peptides derived from proteins degraded in endocytic vesicles. Self-antigens are suppressed by regulatory T cells. $CD4^+$ T cells can also be cytotoxic. MHC class II is also found on cells of the epidermis, both on the residual $CD1a^+$ dendritic cells and on most of the keratinocytes of the basal cell layer.
- **HLAs corresponding to MHC class III:** These encode components of the complements.
- **HLA (MHC) genes**: They are highly polymorphic, which means that they have many different alleles, allowing them to fine-tune the adaptive immune system.

THE MHC—T CELL RECEPTOR INTERACTION

T cells recognize the antigen by their antigen receptors, which are heterodimers of two chains designated as either αβ T cell receptors (TCRs) (the

Table 3.1: Gell and Coombs hypersensitivity reactions associated with various IM-ADR[4]

Gell Coomb class	Immune response	Consequences	Symptoms/ effects	Nature of drug binding	Predominant cells involved
Type I	IgE (soluble antigen)	Mast cell degranulation	Urticaria, anaphylaxis	Covalent drug binding (hapten)	B cells, mast cells
Type II	IgG (cell or matrix associated antigen)	Cytolysis	Immune cytopenias	Covalent drug binding (hapten)	B cells, phagocytes, NK cells
Type III	IgG and complement (soluble antigen)	Immune complex disease (vasculitis)	Serum sickness, Arthus reaction, Vasculitis	Covalent drug binding (hapten)	B cells, phagocytes, NK cells
Type IV a	Th1 (Antigen presented by cells or direct T cell stimulation)	Monocyte activation by IFN –gamma and TNF alpha	Contact dermatitis, Baboon syndrome (SDRIFE)	Covalent and non covalent drug binding	T cells , macrophages/ monocytes
Type IV b	Th2(Antigen presented by cells or direct T cell stimulation)	IL4, IL5, IL13 induced eosinophilic inflammation	Maculopapular exanthema, DRESS	Covalent and non covalent drug binding	T cells, Eosinophils
Type IV c	T- CTL (Cell-associated antigen or direct T cell stimulation)	Perforin and granzyme mediated keratinocyte killing	Maculopapular exanthema, bullous ADR	Covalent and non covalent drug binding	T cells
Type IV d	T cells (Soluble antigen presented by cells or direct T cell stimulation)	Neutrophil recruitment by IL 8, IL-17 GM-CSF	Acute generalized exanthematous pustulosis, Behcet's disease	Covalent and non covalent drug binding	T cells, Neutrophils

T- CTL - (Cytotoxic T lymphocytes); Ig- immunoglobulin; IFN – interferon; TNF – tumor necrosis factor; IL – interleukin, Th- T helper cell; ADR- adverse drug reaction.

majority of T cells) or γδ TCRs (about 5% of circulating T cells). Each T cell displays thousands of identical TCRs, which bind to a bimolecular complex displayed at the surface of the antigen-presenting cell (APC). The antigens (drugs) bound to MHC are presented to the TCR in a peptide bound or a nonpeptide bound manner in the groove of a major MHC molecule. This interaction can be broadly divided into two signals that eventuate into the immune activation process. **Signal 1** comprises the stages of reactive drug metabolite formation, conjugation of drug to protein, and direct interaction of the drug and MHC molecules. **Signal 2** consists of regulation by costimulatory and coinhibitory molecules, which activates various pathways, resulting in the highly variable clinical manifestations of drug hypersensitivity. The heterogeneity in IM-CADR is because of allelic variations in MHC gene complex and the TCR repertoire.[8]

HLA ALLELES AND IM-CADR RISK

Certain adverse drug reactions (ADRs) are strongly associated with variation in the HLA genes (Table 3.2). Examples include associations between carriage of the HLA-B*57:01 allele and abacavir hypersensitivity syndrome, the HLA-B*15:02 allele and carbamazepine (CBZ)-induced SJS/TEN, and the HLA-B* 58:01 allele and allopurinol-induced SJS/TEN, among others. Endogenous peptide-loaded HLA-B*15:02 molecule presents CBZ to cytotoxic T cells without the involvement of intracellular drug metabolism or antigen processing to precipitate SJS/TEN. CBZ could directly interact with the TCR in an *HLA-B*15:02*-restricted manner, in comparison to the abacavir-peptide-*HLA-B*57:01* model [9] as described later in this section. The following are certain characteristics of HLA allele–restricted IM-CADR:

- **Organ specificity:** HLA-B*15:02 is a risk factor in CBZ-induced cutaneous organ disease.
- **Ethnicity specific:** The HLA-associated risk in IM-CADR varies in various ethnic groups. HLA-B*15:02 is a risk factor in CBZ-induced SJS/TEN in Han Chinese, Thai, and Malay patients but not in Northern Europeans. This is explained by the fact that the background prevalence of HLA-B*15:02 varies from 4% to 15% in the affected populations but is less than 1% in Japanese and Korean subjects and extremely rare in Northern Europeans (<0.01%).
- **Same allele, multiple phenotypes:** In HLA-B*3101-positive individuals, CBZ causes TEN, DRESS, and maculopapular exanthema (MPE).

Table 3.2: HLA alleles associated with IM-CADR risk[9]

Drug	Clinical pattern of ADR	HLA association	Ethnicity
Allopurinol	SJS TEN	B*5801	Han Chinese, Thai, European, Italian, Korean
	HSS/DIHS/DRESS	B*5801 (or B*58 haplotype)	Han Chinese, Korean, Japanese, Thai, European
Carbamazepine	SJS TEN	B*1502	Han Chinese, Thai, Malaysian, Indian
		A*3101	Japanese, northern European, Korean
	HSS/DIHS/DRESS	A*3101	Northern European, Japanese, Korean
	Maculopapular exanthem	A*3101	Han Chinese, northern European
Oxcarbazepine	SJS TEN	B*1502 and B*1518	Han Chinese, Taiwanese
Lamotrigine	SJS TEN	B*1502	Han Chinese
		B*38	European
Phenytoin	SJS TEN	B*1502, B*1301, Cw*0801 and DRB1*1602	Han Chinese
Sulphonamides	SJS TEN	A*29, B*12 and DR7	European
	Haplotype Turkish	A*30–B*13–Cw*6	
Oxicam	SJS TEN	B*73, A*2 and B*12	European
Abacavir	HSS	B*5701	European, African
Dapsone	HSS	B*13:01	
Nevirapine	HSS	Cw*8 or CW*8–B*14 haplotype Cw*4 and DRB1*15 B*3505 B*3501 and B*15/DRB1*15	Italian, Japanese Han Chinese Asian Australian
	Delayed rash	DRB1*01 Cw*04	French African, Asian, European, Thai
Efavirenz	Delayed rash	DRB1*01	French
Aminopenicillins	Delayed rash	A*2 and DR*52	Italians
Hydralazine Procainamide, Isoniazid, Methyldopa and Quinidine	Drug induced LE	DR*4	European

SJS – Stevens-Johnson syndrome; TEN – toxic epidermal necrolysis; HSS – hypersensitivity syndrome; LE – lupus erythematosus; NSAID – nonsteroidal anti-inflammatory drugs.

Adapted from: Pavlos R, Mallal S, Phillips E**.** HLA and pharmacogenetics of drug hypersensitivity. *Pharmacogenomics* 2012; 13: 1285–1306.

- **Same HLA allele, different drugs, many organs:** Same HLA allele can be associated with adverse reactions to therapeutically and structurally unrelated compounds but with effects in different organs. For example, HLA-B*57:01 allele is associated with increased risk of both abacavir hypersensitivity and flucloxacillin-induced hepatotoxicity.
- **Many drugs, same organ:** The same type of organ injury can occur with the same HLA allele, even with therapeutically and structurally unrelated compounds. For example, HLA-DRB1*15:01 is associated with liver injury with both lumiracoxib and co-amoxiclav.
- HLA alleles have a high negative predictive value but low positive predictive value (PPV) in relation

to ADRs, suggesting that these allelic markers are necessary but not sufficient to elicit an allergic response. In abacavir hypersensitivity, all reactive patients are positive for HLA-B*5701. The allele presence has 100% negative predictive value in that if the HLA allele is negative, there is no likelihood of drug reaction. This feature makes screening for the risk allele and exclusion of drug therapy for carriers a feasible approach to eliminate these reactions in at-risk populations.

- HLA-B*5701 also has an unusually high PPV of 55% unlike other allele–drug associations, whose PPVs are usually in single digits. That means in 55% of subjects in whom the allele is present will have an ADR, whereas 45% will not. So merely HLA-*5701 testing will deny abacavir therapy to 45% genuine patients who might not react to the drug in the first place.
- Low PPVs are currently the major limiting factor in widespread population use of pharmacogenetic HLA risk allele screening. This indicates that a combination of multiple risk alleles, the stage of disease, viral reactivation status, ethnicity, dosage of medicine, clinical indication of administration of drug and drug metabolism variations (cytochrome polymorphisms) all contribute to a composite risk figure for IM-CADR.

The HLA risk allele strategy has been applied in the clinical setting for abacavir, CBZ, and more recently, allopurinol, with a marked reduction in the incidence of these ADRs.[10]

WHY DO SOME DRUGS CAUSE MULTIPLE DISTINCT TYPES OF CADR?

It is still not known why the same drug, such as amoxicillin or sulfamethoxazole, causes a MPE in one person and AGEP in another. An immunogenetic disposition, such as certain MHC alleles or a polymorphism in the TNF-promoter, may play a role. In addition, the genetic polymorphism of metabolizing enzymes (e.g. of certain cytochrome P450 enzymes or of *N*-acetyltransferase) may contribute to the generation of chemically reactive or toxic compounds, which cause hypersensitivity.[11]

ROLE OF TCR CLONOTYPE IN IM-CADR

Despite the strong HLA predisposition to drug hypersensitivities, it remains unknown whether particular variants of TCR participate in the recognition of small drug/peptide–HLA complexes. Studies identified a dominant TCR clonotype Vb-11-ISGSY from 84% of patients with CBZ-associated SJS/TEN. This TCR was found in only 14% of CBZ-naive healthy control subjects and was absent in CBZ-tolerant patients. Additionally, T cells derived from CBZ-naive, HLA-B* 15:02-positive, and TCR Vb-11-ISGSY-positive patients acquired a cytotoxic phenotype after CBZ exposure in cell culture experiments, which was blocked by the addition of Vb-11-ISGSY-specific antibody.[12] CBZ-specific cytotoxicity could be primed in vitro in the peripheral blood mononuclear cells (PBMCs) of healthy subjects who are carriers of the susceptible HLA allele (HLA-B*15:02) and Vb-11-ISGSY. These studies are the first to identify the concomitant involvement of both a specific HLA allotype and TCR clonotype in the pathogenesis of an IM-CADR. The requirement for both a specific HLA restriction and the use of a specific TCR clonotype that targets a specific pathogen epitope is one potential explanation for the very low PPVs observed for HLA carriage as a predictor of a particular ADR.

THE CELLULAR PLAYERS IN IM-CADR IMMUNOPATHOGENESIS

$CD4^+$ T cells are the predominant population that infiltrates into maculopapular rash skin lesions, and reports have shown also that most drug-specific T cells are $CD4^+$ T cells. However, in severe CADR, $CD8^+$ T cells were found to be the predominant population that infiltrated into the epidermis of skin lesions of SJS/TEN patients. In MPE (but not in AGEP), keratinocytes are stimulated and express MHC class II and are therefore potentially able to present antigens to $CD4^+$ T cells. Interestingly, more $CD8^+$ than $CD4^+$ cells are activated, in spite of a dominant $CD4^+$ cell presence in the affected skin. $CD4^+$ T cells are mainly located in the perivascular dermis, whereas both $CD4^+$ and $CD8^+$ T cells are found at the dermoepidermal junction zone in equal numbers.[13] The immunohistology of mild bullous CADR is actually quite similar to MPE: Massive T cell infiltration, MHC upregulation on keratinocytes and immigrating T cells, and IL-5 expression in the lesions, with the decisive difference that more perforin-positive $CD8^+$ T cells are involved. These $CD8^+$ killer T cells may cause formation of bullae because such cells not only kill MHC class II–bearing keratinocytes but also keratinocytes that express MHC class I.[14] Patients with bullous IM-CADR show strong $CD8^+$ T cell emigration to the epidermis, probably due to preferential presentation of the drug by MHC class I molecules. Two clearly distinct immune reactions might occur simultaneously, as the $CD8^+$ T killer cells found in bullous skin diseases secrete high levels of interferon gamma (IFN-γ), whereas the $CD4^+$ T cells secrete IL-5. Enhanced production of IL-5 by drug-specific T cells is common in different forms of drug allergies. This cytokine is known to be a key factor in regulating the growth, differentiation, and activation

of eosinophils, which frequently are increased in various forms of drug allergies and can be found in the serum during the acute stage.[15] Eosinophils may contribute to the generation of tissue damage by the release of various toxic granule proteins, such as eosinophilic cationic protein, major basic protein, and eosinophil peroxidase; they may also be involved thereby in amplifying the underlying immune response in drug-induced MPE.[16]

AGEP acute lesions typically reveals the presence of intraepidermal pustules, which are filled by neutrophilic leukocytes [polymorphonuclear leukocytes (PMN)] and surrounded by activated HLA-DR-expressing $CD4^+$ and $CD8^+$ T cells. In contrast to MPE and bullous skin reactions, the keratinocytes did not express MHC class II, but showed an elevated expression of the neutrophil attracting chemokine IL-8 (CXCL-8). T cells and neutrophils appear to cooperate, e.g., as in psoriasis, reactive arthritis, or Behcet's disease. Analysis of patch test reactions suggests that drug-specific T cells emigrate first, cause formation of vesicles by killing keratinocytes, and then recruit neutrophilic leukocytes. In addition, the T cells produce high levels of granulocyte–monocyte colony-stimulating factor, which is probably important for the survival of the emigrated neutrophilic leukocytes.[17,18]

Regulatory T cells (T-reg) maintain self-tolerance and suppress immune responses. T-reg have been reported to be involved in the pathogenesis of SJS/TEN. T-reg function is profoundly impaired in TEN, even though the cells are present at normal frequency.[19] These functional defects in TEN are restored upon recovery. These findings indicate that transitory impairment in their function during the acute stage of TEN may relate to severe epidermal damage, whereas a gradual loss of their function after resolution of DIHS may increase the subsequent risk of autoimmune disease occurrence.[20]

The proportion of circulating IL-17-producing $CD4^+$ T cells but not $CD8^+$ T cells is significantly higher in patients with SJS/TEN than in patients with erythema multiforme, as well as in healthy subjects. IL-17-producing $CD4^+$ T cells in a CLA^+CCR4^+ subset with skin-homing properties are found at a significantly higher proportion in this subset of patients with SJS/TEN. The proportion of circulating Th17 cells decreases significantly after disease improvement. Collectively, these results suggest that skin-homing Th17 cells are involved in the pathogenesis of SJS/TEN. Th17 cells may be involved in inflammation and tissue damage in patients with SJS/TEN through regulation of the recruitment of neutrophils and other inflammatory leukocytes.[21]

ROLE OF INNATE IMMUNITY IN IM-CADR (Fig. 3.1)

Patients develop delayed-type drug reactions after a sensitization phase, which lasts normally more than 3–4 days, frequently even longer. This primary sensitization is likely to happen in the lymph nodes. It requires three factors: (1) covalent binding to a protein, which is processed and presents the modified peptide on MHC molecules; alternatively, the drug can bind directly to the MHC–peptide complex, (2) the availability of T cells able to react with the compound be it presented by covalent or non-covalent binding, and (3) an additional "danger" signal (virus, drug metabolite, etc.), which indicates to the immune system to react. To develop an effective immune response against drug, the innate immune system needs to be activated. The innate immune system comprises serum proteins and cells, which provide broad but relatively nonspecific host defenses. These defenses lack the properties of antigenic specificity and immunologic memory that characterize acquired immunity. Important cellular components of innate immunity are APCs such as monocytes, macrophages, and dendritic cells, which need to be activated to appropriately present foreign antigen to the specific immune system. Their engagement may stimulate expression of co-stimulatory molecules and cytokine production, thereby providing important signals to activate resting T cells. Such enhancing factors might be provided by the drug or a drug metabolite itself.[22] Alternatively, the massive stimulation of innate and acquired immune systems during generalized viral infection with HIV, Epstein–Barr virus (EBV), or herpesvirus-6 or during an acute exacerbation of an autoimmune disease (such as Still's disease or systemic lupus erythematosus) may provide sufficient bystander stimulation for the initiation of an immune response to drugs as well, since such patients have a substantially higher frequency of drug allergies.[23-25]

CONCEPTS OF IMMUNOPATHOGENESIS OF IM-ADR[26]

There are three concepts of immunological activation, which are relevant to pathogenesis of IM-ADR, which are described in the following sections, namely the hapten/prohapten concept, pharmacological interactions of drugs with immune receptors (pi concept), and altered peptide repertoire concept.

Hapten/Prohapten Concept

The prototypical reaction that is explained by the hapten/prohapten concept is allergic contact dermatitis. On similar lines, common skin reaction-inducing drugs tend to be small molecules (<500 daltons); thus, they are not antigenic on their own.

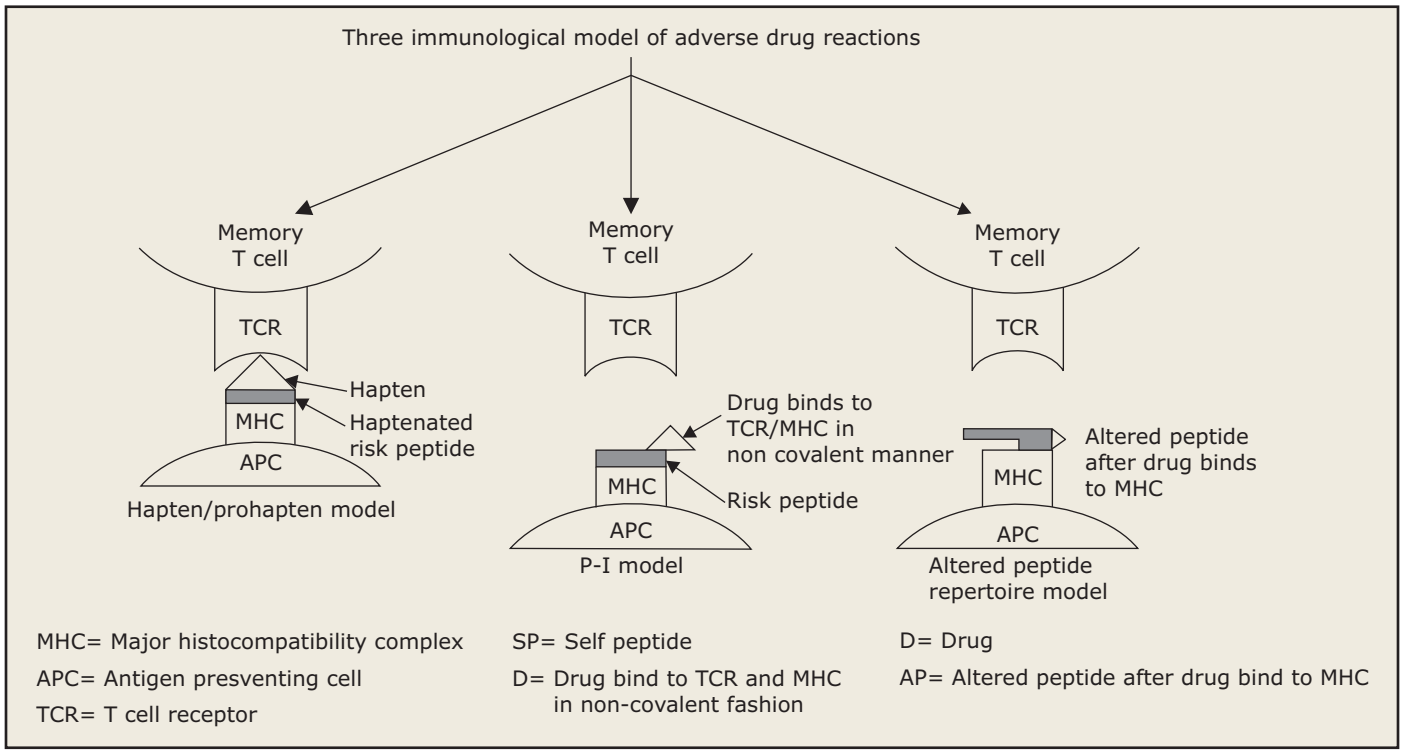

Fig. 3.1: Immunologic models of cutaneous adverse drug reactions.

Three distinct models are proposed to explain immunopathogenesis of CADRs.

1. Hapten prohapten model: Drugs causing ADRs are small molecules which are called haptens which are non-immunogenic by themselves. They are made immunogenic by binding to larger molecules. This covalent complex between drug and peptide is recognized by the T cells through APCs and is usually MHC restricted. Memory T cells are generated in tissue which later produce drug reactions.
2. P-I Model: This concept supports the theory that a drug is able to stimulate T cells directly without forming a hapten in a HLA-dependent manner.

   Under the pi model, the offending drug is postulated to bind noncovalently to either the TCR or MHC protein in a peptide independent manner to directly activate T cells.
3. Altered peptide reportoire model: Peptides associate with HLA molecules by inserting parts of their amino acid residues into a set of six binding pockets in the HLA. This is allele specific. The offending drug occupies a position in the peptide-binding groove of the MHC protein, thereby changing the chemistry of the binding cleft and the peptide specificity of MHC binding. It is proposed that peptides presented in this context are recognized as foreign by the immune system and therefore elicit a T cell response leading onto the drug reaction.

But they are chemically reactive and thus able to undergo stable, covalent binding to a larger protein or peptide. This modification after binding with a protein or peptide makes the peptide moiety immunogenic. This stable covalent binding by a chemically reactive drug to a protein allows the formation of a neoantigen. Cell-bound or soluble immunoglobulins can recognize it directly, whereas T cells recognize a hapten–peptide fragment that is generated by intracellular processing of the hapten–protein complex by APC and is presented to T cells by MHC molecules. This happens in tissue residing APCs as well as in the lymph nodes. Effector T cells (TEff) and T memory cells (TEM) home to where the prohapten/hapten carrier compounds are derived from during primary sensitization.[26,27] The chemical properties of hapten-like drugs are crucial for the generation of antigenic epitopes and the activation of the innate immune system. Haptens have been shown to bind to particular amino acids, e.g., penicillin has a tendency to bind to lysine residues. Hapten drugs can stimulate T cells and B cells and elicit more or less all types of immune reactions.[28] For example, penicillins are reported to cause different antibody-mediated diseases, such as anaphylaxis or hemolytic anemia, but also various T-cell-mediated reactions, such as MPE, DIHS, AGEP, SJS, and even TEN.[29]

Drug hypersensitivity to a hapten–peptide complex is less likely to be HLA restricted, as multiple binding sites in a protein suggest that, after processing, a number of potential drug-bound peptides are available for loading onto different types of HLA alleles. Indeed, there are no proven examples of

hapten-restricted immune responses that are strictly associated with HLA alleles.[26] The prohapten concept proposes that a chemically inert drug (e.g. sulfonamides) may become reactive after undergoing metabolism, and then it is able to form a hapten and stimulate an immune response. Sulfamethoxazole has been proposed as a typical example of a prohapten, as it is not chemically reactive but gains immunogenicity by intracellular metabolism. Cytochrome P450–dependent metabolism can lead to sulfamethoxazole–hydroxylamine, which becomes sulfamethoxazole-nitroso after oxidation, a chemically reactive compound that is able to bind covalently to proteins and peptides. The finding that keratinocytes might also process sulfamethoxazole to sulfamethoxazole–hydroxylamine supports this concept and may explain the manifestation of drug allergy in the skin.[30] It is important to note that neither the hapten nor the prohapten necessarily needs to undergo processing to become antigenic.

Pharmacological Interactions of Drugs with Immune Receptors (p-i Concept)

According to the hapten and prohapten concepts, drugs and other substances that are not chemically active and that are therefore incapable of coupling to a protein would not be antigens and could not induce hypersensitivity reactions. However, this hypothesis has been challenged by clinical and immunological evidence that cannot be explained by hapten or prohapten models. This brings into picture the pi concept that proposes that a drug is able to stimulate T cells directly without forming a hapten, in an HLA-dependent manner. Under the pi model, the offending drug is postulated to bind noncovalently to either the TCR or MHC protein in a peptide independent manner to directly activate T cells.[31] Chemically inert drugs, which are unable to bind covalently to peptides or proteins, can nevertheless activate certain T cells, if they fit with sufficient affinity into some of the various TCR or MHC molecules. The steps involved are as follows: (1) the chemically inert drug binds in a labile way to MHC–peptide complexes (MHC class I or II); (2) T cells screen the MHC molecules and if a TCR fits into the drug–MHC–peptide complex, it binds and receives a signal; (3) the signal is interpreted as immunological as the responsive cell is a T cell. Examples for drugs that act by this model are lidocaine, mepivacaine, celecoxib, lamotrigine, CBZ, and p-phenylenediamine.[32] To induce T cell activation via the pi concept, the following conditions have to be fulfilled, if the stimulation occurs via drug binding to the TCR:

- The T cells express a TCR, into which the drug fits and can induce a stimulatory signal.
- The T cells have a low threshold for activation, which allows them to react to a "minor" signal such as the drug binding to its TCR. Antigen-experienced, memory T cells (TEM) may have these properties.
- In addition to a sufficient drug concentration, APCs with an appropriate MHC are present. Thus, a dense network of T cells and APCs is favorable.[33]

  TEM are highly concentrated in the skin where they may act as "sentinel" cells, rapidly stimulated by antigen penetrating the skin. The drug is bound in a labile way as it can be washed away from the cell surface, in contrast to covalently bound drugs, which cannot. This model has also been hypothesized to explain the in vitro T cell reactivity that has been observed within seconds of drug exposure, a time course that is inconsistent with intracellular antigen processing or for IM-ADRs that are observed after the first encounter with a drug. A drug-reactive T cell clone reacts to the drug within seconds, before metabolism and processing can take place explaining this short period. Evidence for the pi mechanism also lies in observations in which even fixed APC, which are unable to process antigens, are still able to activate specific T cell clones.[34]

Altered Peptide Repertoire Concept

Peptides associate with HLA molecules by inserting parts of their aminoacid residues into a set of six binding pockets in the HLA. The structure of these pockets is highly allele specific, thereby dictating peptide-binding preferences for each HLA molecule. In the altered peptide repertoire model, the offending drug occupies a position in the peptide-binding groove of the MHC protein, thereby changing the chemistry of the binding cleft and the peptide specificity of MHC binding. It is proposed that peptides presented in this context are recognized as foreign by the immune system and therefore elicit a T cell response. It has been demonstrated that a drug can bind directly to the pocket of a specific HLA while not binding to a closely related HLA molecule. Part of the drug protrudes into the HLA molecule's pocket, reducing that pocket's size, which accounts for its preferential binding of smaller amino acids following drug exposure. These data suggest that HLA and the drug form a complex before the HLA molecules are loaded with peptides inside the cell, thereby altering the pool of self-peptides that are bound to the HLA and are displayed on the cell surface for T cell recognition.[35] This shift in the specific HLA-associated cell surface peptide display leads to the activation of different T cells. For example, the activation of a wide range of $CD8^+$ T cells occurs as the cellular basis of abacavir

hypersensitivity reactions. The drug was also shown to bind to aminoacid residues that are unique to the HLA molecule, which would explain the drug's allele specificity. The process involves metabolism-independent, direct, noncovalent, and dose-dependent association of abacavir with amino acids in the HLA-B*57:01 binding cleft. This shift in the bound peptide repertoire is a plausible explanation for drug-induced hypersensitivity.[36]

ROLE OF VIRUS AS AN ANTIGEN

Infectious antigens like viruses may lead to presentation of peptides which are cross-reactive with the TCR specific for certain drugs. As chronic commensal viral infections are a persistent source of stimulation, cross-reactivity between drugs and such viruses might explain why drug-specific T cell reactivity can persist for a very long time even in the absence of the causative drug. A relationship between viral infections and the simultaneous or subsequent development of a drug rash has been observed in a number of clinical situations e.g. the detection of high levels of human herpesvirus 6 (HHV-6) DNA in severe T-cell-mediated drug hypersensitivity syndrome.[37] A new variant of coxsackie virus (CV) A6, in fact causes TEN-like reactions, further strengthening the correlation.[38] The proof of concept was always there in the form of increased proclivity of HIV-positive individuals to have IM-ADR. Penicillins have been known to precipitate MPE in infectious mononucleosis caused by EBV, which resembles drug hypersensitivity.

There are various concepts of the virus–drug duality in pathogenesis of IM-CADR. HHV-6 is commonly reactivated 2–3 weeks after onset of drug hypersensitivity (DRESS), sometimes resulting in relapse of fever and hepatitis. EBV-specific $CD8^+$ T cells were substantially overrepresented within the T cell pool in these reactions. There is a shift in the paradigm from Th2 to Th1 and consequently the decreased total B-lymphocyte counts and serum immunoglobulin levels, which may predispose to viral reactivation. Drugs stimulate T cells that may harbor latent herpes viruses and, when stimulated by the drug, the viral genome is replicated and reactivated in the cell. DRESS also promotes the expansion of regulatory T cell populations (T-reg) that are susceptible to infection by viruses such as HHV-6.[39]

It is also postulated that monomyeloid precursors are decreased in the blood due to conversion to plasmacytoid dendritic cells which home on to the lesional skin, thereby causing a paucity of the former in peripheral circulation, which might also cause HHV-6 reactivation. In addition, herpesviruses have immunotropic properties and modulate immune responses to drugs or directly attack the immune system, thereby increasing IM-ADR risk. Anti-CYP-450 antibodies may be produced because of the cross-reactivity between the viruses and CYP-450 components, thereby disturbing drug metabolism and increasing chances of drug reactions. There are multiple levels of interaction between virus and drugs which deserves to be studied further.

HETEROLOGOUS IMMUNITY MODEL

Our immune system has evolved to contend with the degree of antigenic diversity presented to the human body is through the generation of polyspecific TCRs that are capable of recognizing multiple peptides. Thus, a single TCR might recognize peptides derived from more than a single pathogen, thereby enhancing our immune defenses. This concept is termed heterologous immunity (Fig. 3.2).[40] The concept of heterologous immunity is similar to but distinct from that of direct alloreactivity, a setting in which a cross-reactive TCR recognizes peptide antigen presented in the context of non-self-MHC. Direct alloreactivity is the basis of acute tissue rejection after solid organ transplantation and graft versus host disease after hematopoietic stem cell transplantation.[41] These memory responses are derived, at least in part, from

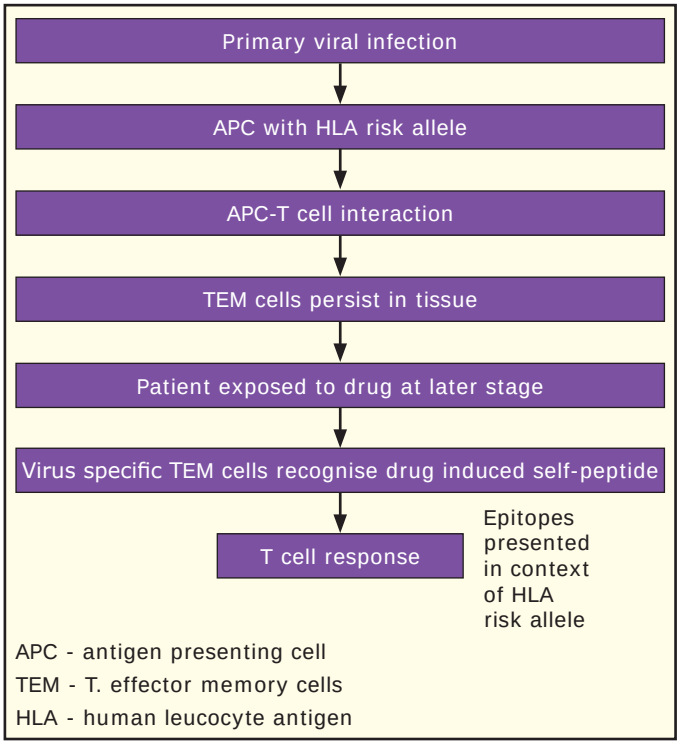

Fig. 3.2: Heterologous immunity model of drug reactions.

Polyspecific T cell receptors (TCRs) that are capable of recognizing multiple peptides are generated during a viral infection. This is followed by Antigen Presenting Cell (APC)- T cell interaction which generates memory T cells called TEM cells. These T Emcells recognise endogenous peptides in the context of drug-HLA complex to result in a T cell response.

heterologous virus-specific memory T cells. Of the viral pathogens that have been shown to be associated with T cell alloreactivity, members of the HHV family have been most frequently observed and best characterized.[39] Heterologous immune responses stem from preexisting memory T cells and that HHV-specific T cells make up a significant proportion of the memory pool. It is possible that preexisting cross-reactive memory $CD8^+$ T cells are pathogenic in cases of early-onset IM-ADRs through the heterologous immunity model.[42]

Salient Features and Steps in the Heterologous Immunity Model[26] (Fig. 3.2)

- First, a prerequisite feature of each T-cell-mediated ADR is carriage of the HLA risk allele.
- Second, the subject acquires primary infection by HHVs (or other pathogen). HHV peptides are presented in the context of the HLA risk allele, and a polyclonal $CD8^+$ T cell response contains the virus. The HHV establishes latency, and the T cell response contracts.
- Third, memory T cells persist at the site of antigen encounter. This cell population is intermittently stimulated by viral antigens during viral reactivation. Activation of TEM cells forces the virus back into latency.
- Fourth, later in life, the subject is exposed to the offending drug. The drug interacts with the pathogenic HLA protein, which results in either neoantigen formation (as might be seen with haptenated peptide), direct activation of T cells, or presentation of an altered repertoire of endogenous peptides.
- Fifth, the peptide–MHC complex is recognized by the TCR that was initially primed against HHV peptide either through molecular mimicry or through an alternate binding strategy. This triggers activation of memory T cells and results in clinical ADRs.
- The cross-reactive T cell clonotype that was initially primed against viral antigen is now activated by the drug–peptide–MHC epitope, and the ensuing immune response is no longer limited to the site of viral reactivation; the relevant antigen is now widely distributed, and the T cell response follows this distribution.
- It is important to note that this model includes two points of HLA restriction: At the initial encounter with pathogen antigen to generate the primary T cell response and then again at the time of endogenous peptide presentation in the setting of drug exposure.
- Viral replication is not required for IM-ADRs under the heterologous immunity model.
- This model needs to be contrasted from HHV reactivation in DRESS/DIHS model, where the virus is not the initiator but is an interim step due to dysregulated immune milieu, which is characteristic of DRESS.
- This model explains why these T cell responses do not wane with time because there exists a persistent source of antigen from a chronic persistent pathogen, such as HHV, that maintains these specific T cell populations.

FUTURE OF THE HETEROLOGOUS IMMUNITY MODEL[26]

Advances in technologies to characterize the TCR repertoire within an individual patient, including deep sequencing techniques that target the TCR Vb genes, ultrasensitive PCR assays to detect and quantify rare TCR variants, and sequencing assays designed to identify paired TCR a- and b-chain sequences, will enable these discoveries. Furthermore, new computational and experimental methods to identify the HLA-restricted HHV epitopes that prime the cross-reactive pathogenic TCRs in these reactions will shed light on the role of heterologous immunity as a mechanism of drug hypersensitivity. Direct evidence for this model is still lacking; however, if proved, it is likely to explain many outstanding observations regarding T–cell-mediated drug hypersensitivity reactions, including the incomplete PPV for HLA association, tissue specificity, short latency period (for some ADR), and long-lasting immunity to drugs in the absence of ongoing exposure.

CONCLUSION

The often surprising appearance of IM-ADR and the multitude of causes have made drug allergy a difficult area of clinical research. Although drug allergies are iatrogenic diseases that are unpredictable and embarrassing to the clinician, it has to be the constant endeavor of immunologic researchers to identify potential risk factors, which are pharmacological, pharmacogenetic, and epigenetic and delineate predictive models, which can help preempt the CADR by personalizing treatment. Chemically inert drugs are immunogenic only because of their structural features, which enable them to interact with immune receptors. These structural features have never been considered in drug development but may account for a substantial proportion of unforeseen side effects and could be and should be incorporated at the time of drug design to improve the safety profile. A detailed knowledge of the various facets of immunopathogenesis of IM-CADR events may provide c and clinical immunology.

LEARNING ESSENTIALS

- Off-target induction of an immune system-mediated reaction is an adverse immunological reaction and is known as a hypersensitivity reaction.
- Type IV reactions are mediated by T lymphocytes and called "delayed type" because they characteristically develop over 24–48 hours following challenge with the causative agent. Type IV reactions have been further subclassified into types IVa–d based on the cytokine profile and the cellular players involved.
- Foreign antigens presented by MHC class I attract $CD8^+$ or cytotoxic T cells, and those antigens presented by MHC class II attract $CD4^+$ T cells and subsequently humoral immunity.
- The heterogeneity in IM-CADR is because of allelic variations in MHC gene complex and the TCR repertoire.
- T-reg function is profoundly impaired in TEN, even though the cells are present at normal frequency.
- To develop an effective immune response against drug, the innate immune system needs to be activated.
- There are three concepts of immunological activation, which are relevant to pathogenesis of IM-CADR, namely, the hapten/prohapten concept, pharmacological interactions of drugs with immune receptors (pi concept), and altered peptide repertoire concept.
- Viruses and drugs both are involved in a complex interplay involving immune modulation, the exact nature of which needs to be studied further.
- Heterologous immunity is a concept in which a single TCR might recognize peptides derived from more than a single pathogen, thereby enhancing human immune defense and can also explain the immunopathogenesis of IM-ADR in a comprehensive manner.

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Chapter

4

Virus–Drug–Host Interactions: Implications in Cutaneous Adverse Drug Reactions

Abhay Mani Martin

SUMMARY

The *role of microbes*, especially viruses, in the genesis of drug reactions has received much attention recently. Predominant among them is the role of some of the Herpesviridae group of viruses—Epstein–Barr virus (EBV), cytomegalovirus (CMV), herpes simplex virus (HSV), varicella zoster virus (VZV), and recently human herpes viruses-6 (HHV-6). Ampicillin rash noted in infectious mononucleosis (EBV) is a classic example of the role of viral illnesses in drug rashes. Instead EBV reactivation has been seen in Stevens–Johnson syndrome (SJS) and fixed drug eruption (FDE), the role of HHV-6 reactivation has been noted in severe drug reactions such as drug-induced hypersensitivity syndrome (DIHS)/drug reactions with eosinophilia and systemic symptoms (DRESS). In the genesis of drug reactions, whether viral reactions are part of the pathogenetic process or mere epiphenomena due to tissue damage remains controversial. The *role of host immunity*, especially resident memory T cells (T_{RM}) (which reside in tissue) and regulatory T (Treg) cells (which are regulators of the T_{RM} cells) in the presence of viruses, has also gained much prominence in the light of new evidences. These T cells primed for viruses cross-react with drug antigens and cause massive activation of the immunologic cascade and thus result in large-scale tissue damage leading to morbidity and mortality. This chapter highlights the complex virus–drug–host interactions in cutaneous adverse drug reactions.

INTRODUCTION

It has long been observed by clinicians and researchers that mere intake of a drug does not lead to a drug reaction. Drug reactions, more often occur in the setting of an infection. The entry of the virus sets off the host immune response mechanisms to be activated. Drug administration in this altered immunologic milieu, in a genetically predisposed individual, sets off a cascade of events which results in a drug reaction.

Of the viruses, reactivation of herpesviridae is most often implicated in most drug reactions. Virus entry leads to activation of Resident memory T cells (T_{RM} cells) and an altered T regulatory cells (Treg) cell function leading to the range of manifestations seen in drug reactions. This complex interaction among the virus, drug antigen, host immunity and genetic predisposition is essential for a drug reaction to occur (Fig. 4.1).

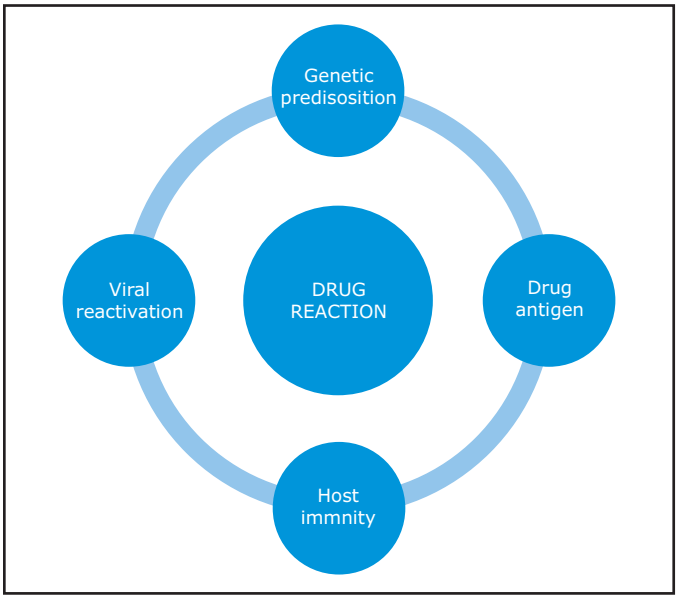


Fig. 4.1: Interaction of various viral, drug and host factors in CADR.

ROLE OF VIRUSES

Viruses have been speculated to play a role in drug reactions, but have never been emphatically proven. In 1967, Pullen et al.[1] noted hypersensitivity to antibacterial drugs in patients with infectious mononucleosis (IM). In 1984, Levy hypothesized that individuals infected with viruses are predisposed to develop adverse drug reactions (ADRs)—quoting the examples of ampicillin-induced rash in IM, Reye's syndrome following influenza and varicella, and virus-aggravated drug-induced agranulocytosis.[2] Since then, there is increasing circumstantial evidence being published to support the fact that exposure to viruses prior to or concurrent with the exposure to drugs can modify the course and outcome of drug reactions. The association of a specific virus to a specific drug reaction or pattern is elusive and hence the association between virus and drug rash is hotly contested.

Human herpes viruses (HHVs) are the major group of viruses implicated, of which Epstein–Barr virus (EBV), cytomegalovirus (CMV), herpes simplex virus (HSV), varicella zoster virus (VZV), and HHV-6 are proven associations.[3] The incidence of drug reactions is greater in individuals with HIV infection too. Herpes viruses are more often associated with drug reactions than other groups of viruses and this could be because of its ability to infect the general population in large numbers, as well as its potential to exist in a latent phase in the host and reactivate itself in immunosuppressed states. Landmark studies by groups led by Shiohara[4] and by Hashimoto[5] with their identification of HHV-6 in drug-induced hypersensitivity syndrome (DIHS)/drug reactions with eosinophilia and systemic symptoms (DRESS) have put viruses back on the radar with regard to drug reaction pathogenesis. The role of different viruses has been proposed in a variety of CADRs (Table 4.1).

Table 4.1: Various CADRs and implicated viruses

Cutaneous ADR	Virus(es) implicated
FDE	HSV
IM	EBV
DIHS/DRESS	HHV-6 EBV, CMV
SJS/TEN	HSV, EBV, CMV, HHV-6, HHV-7
HIV	HSV, EBV, CMV, HHV-6,7, and 8

FDE - Fixed Drug eruption; IM - Infectious mononucleosis; DIHS/DRESS - Drug induced hypersensitivity syndrome/ Drug reaction with eosinophilia and systemic symptoms; SJS/TEN - Stevens-Johnson Syndrome/Toxic Epidermal necrolysis; HIV-Human Immunodeficiency syndrome - HSV-Herpes Simplex Virus; EBV - Epstein Barr Virus; CMV - Cytomegalovirus; HHV - Human Herpesvirus.

Role of EBV in Ampicillin-Induced Rashes in IM

EBV is the causative agent of IM and the disease is characterized by fever, lymphadenopathy, fatigue, and pharyngitis. A diffuse maculopapular rash that occurs around 2 weeks after the administration of ampicillin was first reported by Pullen and is noted often in clinical practice in IM (Fig. 4.2). The incidence of ampicillin-associated rashes in IM ranges from 42% to 100%.[3]

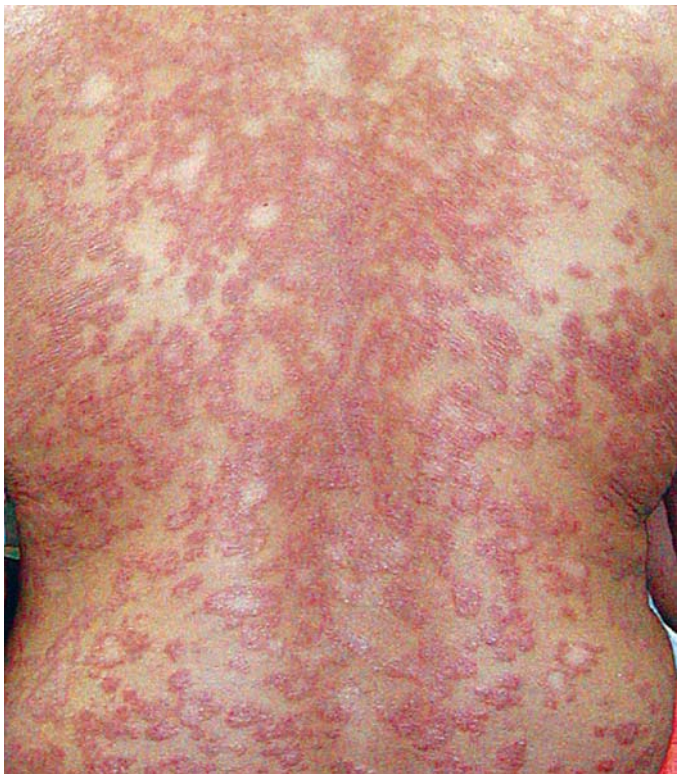


Fig. 4.2: Exanthematous rash to ampicillin in a patient of IM.

However, there is a contrary view that the rash may not be related to ampicillin, and that it could well be part of a spectrum of the disease itself. This maculopapular exanthem has also been reported with other drugs like amoxicillin,[6] azithromycin,[7] quinolones,[8] penicillin G, and tetracyclines.[9–11] Nazareth recognized that, unlike other drugs, the sensitivity occurring with administration of ampicillin in patients with IM is not permanent.[3] Further, it was noted that only 10% of those individuals who had a suspected "ampicillin rash in IM" subsequently had sensitivity to ampicillin, on oral rechallenge, after recovery from the illness. This is comparable to the general population. This indicates that ampicillin is not the sole factor for the rash.

The exact mechanism by which ampicillin causes such a rash in patients with IM is elusive. Investigators

have attempted to identify whether the eruption is a true immunologic reaction to the drug itself or to some other aspect of the immunologic response of the host to the EBV. McKenzie et al.[12] stated that ampicillin rash in IM resulted from a disseminated reaction of the small blood vessels to circulating ampicillin–antibody complexes. They detected elevated antibody-like activity against ampicillin, of both IgM and IgG immunoglobulin classes, by means of a sensitive radioimmunoassay.

Patients suffering from IM show an abnormal clonal expansion of $CD8^+$ T cells. $CD8^+$ T cells, particularly those expressing human leucocyte antigen-antigen D related (HLA-DR) and CD38, are seen in 70% of acute cases. The patients in the acute phase of the disease who are symptomatic show massive clonal expansion of $CD8^+$ T cells, indicating that symptom severity can be correlated with this clonal expansion. It is not completely understood how abnormally expanded T cells, particularly $CD8^+$ T cells, can interact with the drug in IM.[4] It is also unclear as to why all patients who suffer from the disease do not develop rashes on exposure to ampicillin. It is postulated that it relates to the extent to which the expanded $CD8^+$ T cells can cross-react with the administered ampicillin. Such cross-reactivity can also occur with EBV-associated $CD4^+$ T cells. This cross-reactivity of expanded $CD8^+$ T cells explains why certain HLA-B allele–bearing individuals are predisposed to severe drug reactions in association with viral infections.

Other mechanisms have also been suggested for the viral activation of drug rash. Transient loss of immunologic tolerance was propounded by Jappe et al.[13.] Molecular mimicry between drug and viral molecules and high affinity of β-lactams to viral proteins were suggested by Ónodi-Nagy et al.[14] Viral activation may serve as a cofactor for drug-specific T cells. Another postulated theory is that loss of detoxification mechanisms during IM, akin to low glutathione levels in HIV, could be responsible for the drug reaction.

Role of Viruses in Stevens–Johnson Syndrome and Toxic Epidermal Necrosis

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous ADRs that are known to cause extensive skin rashes and are prone to systemic consequences and mortality. T he role of drugs has been well proven in the etiology of the disease. Anticonvulsants, analgesics, and antibiotics are the commonly encountered drug etiologies. Anti-HIV drugs and allopurinol are also known to cause SJS/TEN.[15]

Microbial etiology has been proposed by some authors for the modification of drug-induced SJS/TEN. Bacteria such as *Mycoplasma pneumoniae* was proposed in some studies.[16–18] The role of Herpesviridae group of viruses in the etiopathogenesis of the disease was later suggested by investigators such as Shiohara and Kano.[3] They also suggest that the high incidence of SJS/TEN in patients with HIV/AIDS is attributable to the reactivation of these viruses (especially EBV, CMV, and HSV).

Proposed Mechanisms

EBV and HSV are important opportunistic viruses that affect large populations and have the ability to persist in latent states. They are known to cause large clonal expansions of cross-reactive memory T cell populations.[3] This makes immunologic reactions to the drugs more likely. It is postulated that such cross-reactive memory T cells interact with drugs or drug metabolites and can also alter drug pharmacokinetics. Viral infections can also alter drug presentation to dendritic cells by lymphocytes.[19]

The evidences for the *role of HSV* in the etiopathogenesis of SJS include a history of antecedent infection with HSV, identification of HSV-specific IgG antibodies, and a significant increase in HSV-specific IgG titers during the course of SJS.[3] Surprisingly, HSV DNA was not detected in any of the blood samples, sequentially obtained from patients with SJS. However, longitudinal studies of HSV viral loads have rarely been performed. One such study conducted by Ishida et al.[20] compared EBV, CMV, HHV-6, HHV-7, and HSV DNA levels in the blood sequentially obtained from patients with SJS at or near the time of the initial presentation, before therapy. Increased EBV DNA loads, defined as >200 genome copies/10^6 leukocytes, were detected within 10 days of onset of rash, in half the patients with SJS (40% in cases before systemic corticosteroids). This was in contrast with the DNA loads seen in TEN (<20% of patients) and DIHS/DRESS (<10% of patients). EBV DNA in patients with SJS was detected as early as day 3 of skin rashes. In most of these cases, the highest EBV load was observed at the time of the initial presentation of the SJS and gradually fell to undetectable levels after resolution of clinical symptoms.

These results indicate that EBV reactivation occurs early in the course of an ongoing immune response to drug. This study also noted that EBV loads were lower in those patients who were administered steroids in comparison to those who were not administered steroids, whereas CMV and HHV-6 DNA were more in the steroid-treated group suggesting that steroid can suppress EBV reactivation and its attendant consequences. Further, the study also pointed out that

EBV titers persist even during remission of SJS, raising the possibility that SJS develops in those patients who are not able to mount an immune response to the reactivating EBV.

CMV and HHV-6 were also monitored in this study. CMV viral loads were elevated in the SJS group, but only marginally, compared to the DIHS/DRESS group (22.2% vs 17.6%). No cases of HHV-6 were noted in patients with SJS. A synergism between the two herpes viruses (HSV and EBV) has also been suggested by Shiohara and his group as being responsible for the pathogenesis of SJS.[6]

HIV Infection and Drug Reactions—A Role for Opportunistic Virus Reactivation

Patients with HIV are known to have a higher incidence of ADRs compared to the general population.[21] Viral factors, host immunity, and drug-related factors contribute to this.

These patients are administered a host of drugs (anti-HIV drugs as well as drugs for opportunistic infections), which places them in a vulnerable state for drug reactions. The quantum of exposure to drug antigens is high. Also, the deranged drug pharmacokinetic and pharmacodynamic mechanisms due to altered hepatic and renal metabolism make them prone to drug reactions.

These patients are prone to opportunistic infections, and viruses are an important subset in this group. The incidence of infection with herpesviridae group (EBV, CMV, HHV-6, 7, and 8) is high in patients with HIV, as the lowered immunity provides a right environment for reactivation of latent viruses. This generates heterophile memory T cells, which can cross-react with drug antigens. The complex interaction of viral pathogens with the host immune system makes the host prone for a cross-reactive pool of memory T cells to be generated, resulting in a host of allergic, autoimmune, and neoplastic disorders. These memory T cells primed for reactivity against viruses share antigenic proteins with drug antigens and hence make the host vulnerable for autoreactivity. The incidence of these immune-mediated ailments increases with the fall in CD4 counts and the rise in HIV viral loads.

Altered immunological profiles accompanied by derangement of tolerance mechanisms cause a shift in the profile to autoimmune and neoplastic profiles. The use of multiple drugs exposes the host immune system to multiple drug antigens.

HHV-6 and DIHS/DRESS Syndrome

DIHS is a life-threatening, multiorgan systemic drug reaction pattern characterized by rash, fever, lymphadenopathy, hepatitis, and leukocytosis with eosinophilia.[22] DIHS/DRESS has an incubation period of 3 weeks to 3 months after the intake of drug. Anticonvulsants (carbamazepine, phenytoin, and phenobarbital) are the most common group of drugs causing the disease. Other drugs reported to cause this reaction pattern include allopurinol, dapsone, salazopyrin, mexiletine, and minoxidil.

Viral reactivations have been reported in this disease. HHV-6 is the most common virus noted to be reactivated, though other herpesviridae like EBV[23], CMV[24], and HHV-7[25] have also been reported. Sequential reactivation of these viruses is a feature noted by the Japanese study groups[26] and is analogous to reactivation that occurs in the setting of graft-versus-host disease (GVHD). The etiologic role for HHV-6 virus has been postulated based on the following evidences:

1. Identification of HHV-6 DNA in samples, 2–3 weeks after onset of rash.
2. Detection of rising titers of serum HHV-6 IgG levels.
3. Lack of detection of the virus in other drug eruptions.

DIHS/DRESS has similarities with GVHD that include the mode of clinical presentation, the marked hypergammaglobulinemia, and the sequential reactivation of herpesviridae viruses, namely EBV, CMV, and HHV-6. Further, the complications are similar and include de novo induction of autoimmune disorders or exacerbation of preexisting autoimmune disorders like thyroid or articular disorders. These effects are attributable to both the immunosuppressed state and the reactivation of herpes viruses. Yoshikawa[27] reported that HHV-6 viremia can be detected 2–4 weeks after the bone marrow transplantation, which is similar to the time gap noted in DIHS by Kano et al.[26] Syndrome of inappropriate antidiuretic hormone secretion (SIADH), a complication noted with stem cell transplantation and GVHD associated with HHV-6 reactivation has also been noted with DIHS/DRESS syndrome. Reactivation of herpes viruses can cause limbic encephalitis and resultant SIADH in patients with DIHS/DRESS syndrome. Though drugs like carbamazepine themselves are known to cause SIADH, viral infections are one of the most common causes of SIADH. Hence, one should consider these reactivated viruses as contributory, at least in part, to the SIADH, noted with carbamazepine-induced DIHS/DRESS.

However, an Indian study, conducted by Sasidharan-pillai et al.[28], on reactivation of herpes viruses in

cutaneous ADRs could not demonstrate this correlation. Of the 20 patients, four patients had DRESS syndrome and only one patient turned positive for HHV-6.

Fixed Drug Eruption and Viral Reactivation

Fixed drug eruption (FDE) is a unique drug reaction characterized by a solitary or a small number of pruritic, well-circumscribed, erythematous macules that evolve into edematous plaques; these lesions typically recur at exactly the same sites with each administration of the causative drug, but upon the discontinuation resolve spontaneously, leaving hyperpigmentation. After clinical resolution, the lesions remain quiescent and typically present as gray–brown macules or plaques on the skin, mucous membranes, or on both, for prolonged periods. A burning sensation often precedes the reappearance of these lesions when the causative drug is given.
HSV reactivation has been linked to FDE. The sites affected by FDE such as lips, palms, soles, glans penis, and groin are also targets for HSV infection. Shiohara and coworkers have noted that a vast majority of patients affected by FDE are anti-HSV-IgG seropositive with no clinical symptoms previously.[29] It is postulated that several intraepidermal $CD8^+$ T cells found in FDE on histopathology and immunoperoxidase staining may be effector T cells that had been recruited at the site for combating HSV. Reactivation of the virus leads to activation of these resident T cells thereby causing immune-mediated tissue destruction.[29] The tissue destruction is mediated by interferon gamma (IFN-γ) as well as through direct cytolysis.

ROLE OF HOST IMMUNITY

To understand how a drug reaction can be influenced by a viral infection, one must understand how the immune system tackles the clearance of virally infected cells.

The host immune system responds to viral infections with the generation of T cells. These T cells are subgrouped into *T effector cells* (*Teff cells*), *Treg cells*, *cytotoxic* or *natural killer* (*NK*) *cells*, and *memory T cells* (Fig. 4.3A).

Memory T cells are further divided into *central memory T cells* (T_{CM}), *effector memory T cells* (T_{EM}), and *resident memory T cells* (T_{RM}).

Treg cells are subdivided into *FOXP3*$^+$ and *FOXP3*$^-$ *regulatory Treg cells*.

Role of T_{RM} Cells[30] (Fig. 4.3B)

Studies have shown that after clearance of a viral infection from the skin (e.g. HSV), some T cells are retained at the site of original infection as memory T cells, and these are called T_{RM} cells. These T_{RM} cells are recruited at the infected site when reexposed to the same viral antigen. These cells, once recruited at this site, can "migrate" between keratinocytes, as well as migrate toward another site (elsewhere in the body) and produce effector cytokines such as IFN-γ, to serve as protection against viruses during future attacks by the same virus. These T_{RM} cells reside at the site of infection for 4–6 months after the viral episode is over. They are distributed not only at the initial site of affection but also on the entire skin surface so as to provide antiviral protection anywhere on the skin surface on reinfection by the same virus. These T_{RM} cells decide whether the consequence of the infection is viral control, viral latency or viral lethality, and tissue damage. These virus-specific T_{RM} cells can help contain the infection process when released in small doses. In higher doses, they cause tissue damage. In diseases like FDE, there is high localization of these $CD8^+$ T_{RM} cells at the quiescent site or resting lesions.[16] These cells may have been recruited originally as protection against reinfection by the herpes viruses. These $CD8^+$ T_{RM} cells express broad cross-reactivity and recognize the drug antigen. This results in the cascade of events that result in widespread damage to the keratinocytes resulting in damage to the epidermis.

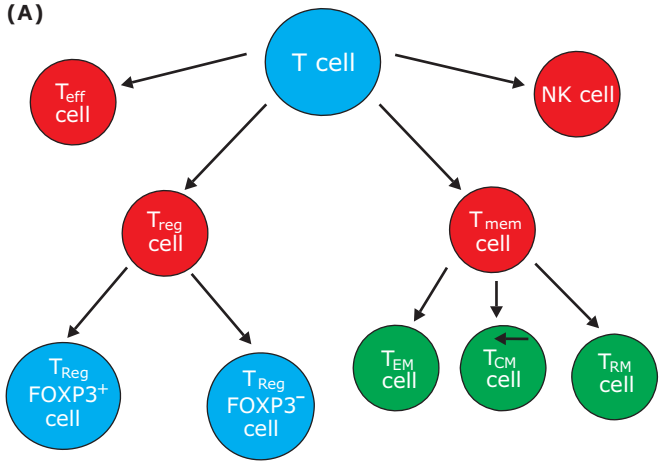
Role of Treg Cells (Fig. 4.3C)

$FOXP3^+$Treg cells are regulatory cells that control $CD8^+$ T_{RM} and T_{CM} cells from overfiring. These cells are recruited to the sites of FDE to restrict the progression of inflammation at the site of drug reactions. Defects that occur in these Treg cells contribute to the spread of the inflammatory process. *The FOXP3*$^+$ *Treg cells are concentrated at the margins of the FDE or TEN lesions.*[17] *The high density (of FOXP3+ Treg cells) at the margins of FDE lesions explains why the FDE lesions are well defined. In contrast, TEN lesions have lower density of these cells and hence have poorly defined margins.*

Treg cells are impaired in function in the acute phase of infections due to viruses such as VZV and parvovirus B19 as shown in the study by Shiohara et al. A similar dampened Treg cell function was noticeable in patients with TEN.[19] This explains the progression of tissue damage in both cases. In contrast to the reduced Treg cell function in the acute phase of the disease in these viral infections, mycoplasma pneumonia is known to cause prolonged Treg cell suppression up to 1 year after clinical resolution.

It can be postulated that *a defective function of Treg*

(A)



T cells are subgrouped into:

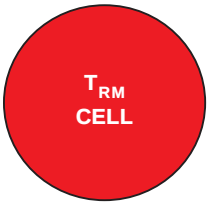
- T effector cells (T_{eff} cells)
- T regulatory cells (T_{reg} cells)
- Cytotoxic or natural killer cells (NK)
- Memory T cells

Memory T cells are further divided:

- Central memory T cells (T_{CM})
- Effector memory T cells (T_{EM})
- Resident memory T cells (T_{RM})

Regulatory T cells are subdivided into FOXP3$^+$ and FOXP3$^-$ regulatory cells (T_{reg})

(B)



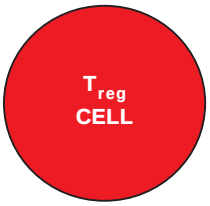
After clearance of a viral infection from the skin (e.g. HSV), some T cells are retained at the site of original infection as memory T cells, and these are called resident memory T cells (T_{RM}).

These T_{RM} cells-

- Are recruited at the infected site when reexposed to the same viral antigen.
- Can "migrate" between keratinocytes as well as to distant sites in the body.
- Produce effector cytokines such as IFN–γ, to serve as protection against viruses during future attacks by the same virus.
- Decide whether the consequence of the infection is viral control, viral latency or viral lethality and tissue damage.

In diseases like FDE, there is high localization of these CD 8+T_{RM} cells at the quiescent site or resting lesions. They express broad cross reactivity and recognise the drug antigen. This results in the cascade of events that result in widespread damage to the keratinocytes resulting in damage to the epidermis.

(C)



Regulatory T cells are subdivided into FOXP3$^+$ and FOXP3$^-$ regulatory cells (T_{reg}).

- FOX3$^+$ T_{reg} cells are regulatory cells that control CD8$^+$ T_{RM} and T CM cells from overfiring.
- Treg cells are impaired in function in the acute phase of infections.
- Defects that occur in these T_{reg} cells contribute to the spread of the inflammatory process.

The FOXP3$^+$ T_{reg} cells are concentrated at the margins of the FDE or TEN lesions.

The high density at the margins of FDE lesions and poor density in TEN lesions explains why FDE lesions are well defined while the TEN lesions have poorly defined margins.

Fig. 4.3: (A) Subtypes of T-cells in the immune system; (B) Role of resident memory T-cell in virus-drug-host interaction; (C) Role of regulatory T-cell in virus-drug-host interaction.

cells (akin to that seen in the acute phase of viral infections and the acute and resolution phases of mycoplasma pneumonia) can explain the propensity to drug reactions. Drug-specific T cells are likely to be unrestricted, due to lowered activation thresholds and defective suppression of their activity.

Thus, in summary, in certain drug reactions, there is massive recruitment of T_{RM} cells (which were primed for viral infection initially) that turn on a cascade of cytokine events that cause tissue damage and destruction. However, this is also coupled by a defective function of Treg cells that normally downregulate T_{RM} and T_{CM} cell function (thereby preventing their overactivity).

The role of host immunity, especially the memory T cells and Treg cells, in viral infections and in drug reactions is summarized in Fig. 4.4.

IMPLICATIONS FOR THE CLINICIAN

Research is on, to explore the etiopathogenetic role of viral antigens and virus reactivation in the pathogenesis of drug reactions. *It is now recognized that there is a complex interplay between genetic*

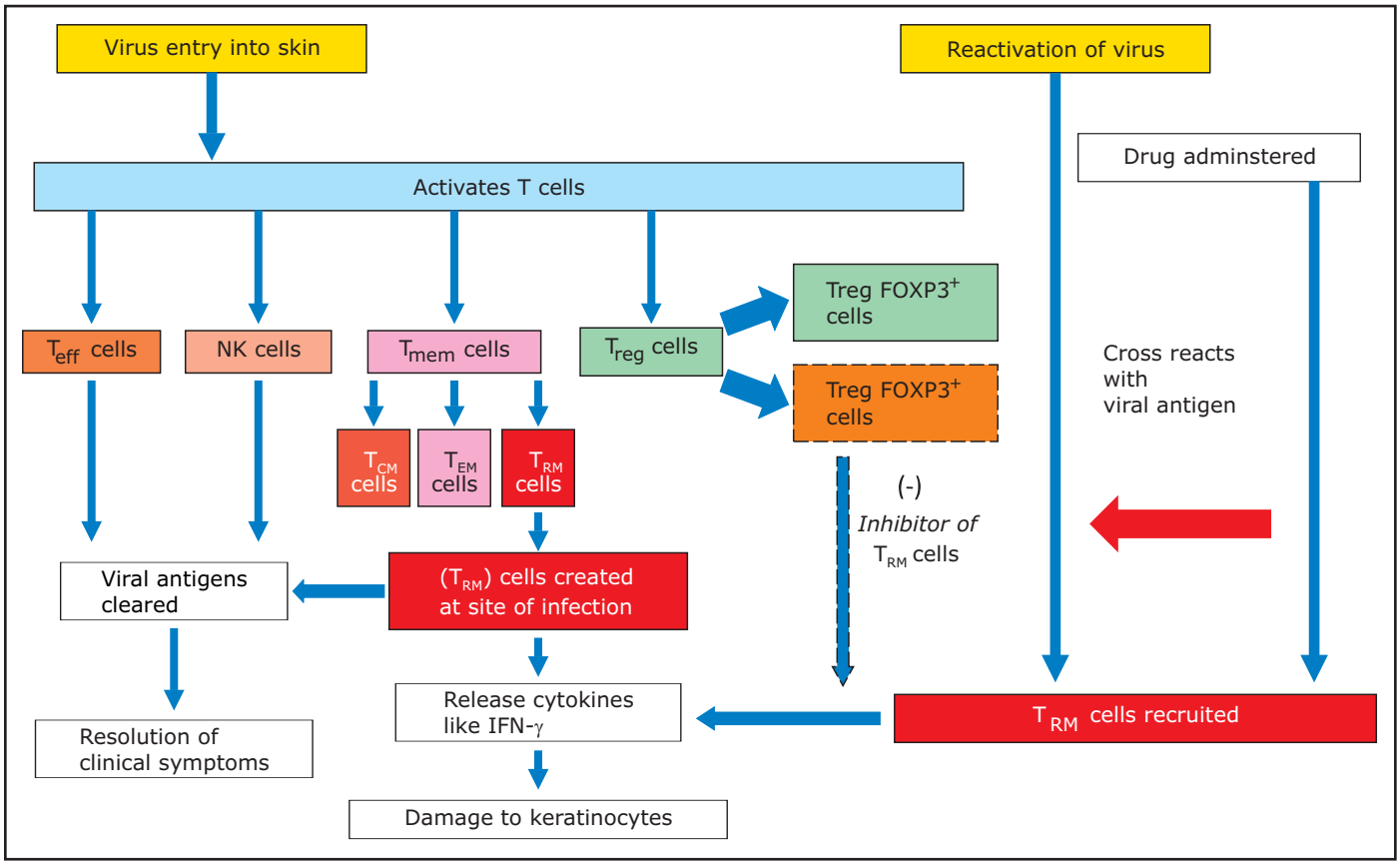


Fig. 4.4: Immunological cascade in virus-drug-host interactions in CADR.

There is activation of resident memory T cells (T_{RM}) when there is viral reactivation and this decides viral control, viral latency or viral lethality and tissue damage. The release of cytokines like IFN –γ causes viral clearance while also causing keratinocyte damage. When severe drug reactions occur, there is cross reaction with viral antigens and thereby massive recruitment of T_{RM} cells. This leads to large scale destruction of tissue. Further there is down regulation of Fox P3 $^{-}$Treg cells. This sets of an unchecked multiplication of T_{RM} cells thus causing tissue damage or lethality. FDE is a prototype where this pattern is exemplified.

T_{eff} - T effector cells; NK cells - natural killer cells; T_{mem} cells - memory T cells; T_{reg} cells - regulatory T cells; Fox P3 + and Fox P3-cells are types of T_{reg} cells; T_{CM} - central memory T cells; T_{EM} - effector memory T cells; T_{RM} cells - resident memory T cells.

predisposition, drug antigen, viral reactivation, and host immunity factors (Fig. 4.1). The above findings are matters of relevance not just to researchers but to clinicians too. The following clinical evidences point to the importance of viral infection, latency, and reactivation in the causation or potentiation of drug reactions as well as the inseparable role of host immunity in this process.

1. *Viral reactivation explains the pathogenesis and clinical presentation of FDE.*

   FDE is a unique drug reaction. The mechanism of how FDE recurrences occur is a matter of discussion and dissent. Viral reactivation of HSV is the basis for the viral hypothesis. Studies have recorded that FDE lesions correlate with HSV reactivations. This is mediated by cross-reacting antigens that activate resident memory T cells, which in turn cause tissue damage. This tissue damage induced by T_{RM} cells is countered by Treg cell activity, which restricts the overactivity of T_{RM} cells. Thus, effective Treg cell activity leads to good resolution of symptoms (as T_{RM} cell–induced immune damage is well controlled), whereas impaired Treg cell activity leads to continued T_{RM} cell–mediated tissue damage leading onto edema, bulla formation, and residual pigmentation.

2. *The morphology of lesions of drug rash overlap in many instances, but have varying degrees of severity, which can be explained by host immune response.*

   Bullous FDE and TEN have similar morphologies at presentation. The localization of the rash in FDE and the spread of the rash in TEN are best explained by the prominent role of Treg cells and T_{RM} cells activated during virus illnesses. Treg cells are present in large numbers at the

periphery in FDE lesions suggesting that they prevent overactivity of the T_{RM} cells, thus causing limitation of tissue damage. This in turn limits the progression of the rash in FDE. On the contrary, the inadequacy of Treg cells would cause an overactivity of cytotoxic T cells thereby causing widespread cytolytic damage to the skin tissue in TEN.

3. *Herpes virus have latent, active, and reactivated states and can influence drug reactions.*

   The role of herpesviridae viruses in the modification of drug reactions has opened newer insights into the study of pathogenesis of drug reactions. Herpes virus infections are common in the general population and exist in active, latent, or reactivated states. The prominent herpesviridae viruses known to reactivate include HSV, EBV, HHV-6, and CMV. The role of these viruses in FDE, SJS, and DIHS/DRESS syndromes has been elucidated earlier in the chapter. Clinicians would be wise to look for preexisting or reactivated viral infections in the setting of suspected drug reactions. Testing for viral markers, in the form of rising antibody titers (e.g. EBV viral capsid IgG titer), and DNA PCR studies of the suspected viruses are not in vogue. However, a day may not be far when such studies will from part of routine workup of suspected drug reactions.

4. *In DIHS/DRESS syndrome, several of the unique clinical features could be explained based on the viral reactivation theory.*

   a. There is a paradoxical lack of remission of the rash in DIHS/DRESS in spite of withdrawal of the incriminated drug. This is attributed to the viral reactivations of EBV, CMV, and HHV-6 in a sequential manner.

   b. The repetitive disease exacerbations noted with this disease is attributed to the virus reactivations. It is not uncommon to find in DIHS recovery of one organ system and involvement of other, probably as a result of sequential viral reactivation.

   c. Patients with DIHS/DRESS are prone to autoimmune disorders like thyroiditis and diabetes mellitus. This has been attributed again to the reactivation of viruses, which can increase the risk of autoimmunity by two mechanisms—"molecular mimicry" (cross-reaction between viral epitopes and host self-antigens) and "bystander activation" (this involves viral activation of innate immune response which release cytokines through upregulation of costimulatory molecules and self-antigens; these cytokines cause activation of dormant autoreactive T cells). These two mechanisms act synergistically rather than sequentially or separately.

   d. The clinical presentation of DIHS/DRESS is similar to acute viral exanthema and is difficult to diagnose even to the trained eye. This similarity could be explained by reactivation of virus rather than the drug administration alone. Further, HHV-6 and other herpesviridae may reactivate when drug is administered. Use of steroids is effective to suppress the symptoms of viral reactivation and progression of drug reactions.

LEARNING ESSENTIALS

- The close interaction between drug, host immunity, and viral reactivations is a matter of intense research and debate.
- The propensity for genetically predisposed individuals to have drug reactions is potentiated by the ability of viruses to reactivate and modified by the host response to these viruses.
- Awareness that viruses, especially herpesviridae group, are relevant in the etiopathogenesis of drug reactions makes the understanding of drug reactions less of an enigma.
- More evidence needs to be gathered to clearly define the role of viruses in drug reactions.

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Chapter

5

Pharmacogenomics and Cutaneous Adverse Drug Reactions: From Bench to Bedside

Amrita Sil • Avijit Hazra • Nilay Kanti Das

SUMMARY

Pharmacogenomics is the study of drug response based on individual's genetic makeup. Although pharmacogenetics and pharmacogenomics are often used interchangeably, the former focuses on single drug–gene interactions, whereas the latter adopts a more genome-wide association approach and deals with the effects of multiple genes on drug response. By adopting pharmacogenetic concepts, it may be possible to render "personalized or precision therapy" instead of "one-dose-fits-all" approach, ensure optimum treatment outcomes, and prevent adverse drug reactions (ADRs) in future. The high level of morbidity and mortality associated with cutaneous adverse drug reactions (CADRs) is a major concern to the physician and patient alike. Such type B ADRs are difficult to predict. Knowledge regarding association of human leukocyte antigen (HLA) and CADRs has been gained for specific drugs such as carbamazepine, allopurinol, nevirapine, abacavir, phenytoin, and lamotrigine. However, different ethnic groups show variations in these genetic associations, probably due to differences in the allele frequency in different populations. Pharmacogenetic screening based on these associations has been developed, which might help to avoid CADRs in at-risk population.

INTRODUCTION

The history of pharmacogenetics dates back to 510 BC when Pythagoras noted that fava beans ingestion resulted in a potentially fatal reaction in some, but not all, individuals.[1] This was later attributed to the deficiency of glucose-6-phosphate dehydrogenase (G6PD) and was named "favism". Also, succinylcholine caused prolonged apnea in patients who were deficient in pseudocholinesterase. Archibald Garrod in 1902 while studying alkaptonuria postulated genetic differences in biochemical process of enzymes to be the cause of adverse reactions and thus laid the basis of pharmacogenetics.[2] Variation within the human genome is seen about every 500–1000 bases.[3] Variability in genetic factors may be concerned with drug-metabolizing enzymes [cytochrome P450, thiopurine S-methyltransferase (TPMT)], drug receptors, drug transporters [ATP-binding cassette (ABC) protein, influx transporter solute carrier(SLC)], human leukocyte antigen (HLA,) or indirect effect of other proteins.

Pharmacogenetics is the study of the genetic basis for variability of drug response including disposition, safety, tolerability, and efficacy. It deals with the genetic influences on drug action as well as drug handling by the body. Pharmacogenomics goes a step further to use this genetic information to guide the choice of drug and dose on individual basis, giving rise to the concept of "personalized medicine" or "tailor-made drugs".[4,5]

Germline genetic mutations, be it in the drug-metabolizing enzymes, drug transporters, drug targets, or HLA, are reportedly responsible for many of the observed inter-individual differences in drug efficacy and the risk of ADRs. With the knowledge gained from the Human Genome Project, pharmacogenomics-based personalized medicine has the potential to transform patient care. The ability to predict susceptibility to severe adverse drug reactions (ADRs) would prevent drug administration to high-risk patients. This would save lives and largely reduce the burden of caring for patients with unexpected drug toxicities. Box 5.1 highlights some terms related to pharmacogenetics.

Box 5.1: Terminology used in pharmacogenetics

Glossary

Allele: A part of the gene that is one member of a pair, located on one of the chromosomes. One allele of a gene is inherited from each parent e.g. B, b.

Haplotype: Haploid genotype. Combination of alleles at multiple loci on the same chromosome transmitted together.

Allozyme: Alternate versions of an enzyme determined by genetic variants(alleles) present at a genetic locus.

Polymorphism: A variation in the DNA sequence that occurs at an allele frequency of >1% in a population.

Single-nucleotide polymorphism (SNP): A single-nucleotide variation in a genetic sequence; a common form of variation in the human genome.

Mutation: A heritable change in the genetic material.

Odds ratio (OR): A measure of association between an exposure and an outcome. The OR represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure. If OR is >1, exposure is associated with higher odds of outcome.

ADVERSE DRUG REACTIONS: THE BURDEN

ADRs are a major clinical problem that accounts for 6.7% of all hospitalizations and rank between the fourth and sixth most common cause of inpatient death in western countries, posing challenges to the health-care system in terms of both patient well-being and medical costs.[6,7] ADRs are also a major burden for the pharmaceutical industry. From 1990 to 2012, there were 43 drug withdrawals from the market due to severe ADRs.[8] ADRs are often classified into two groups. Type A reactions are predictable from the pharmacological mechanisms and are often dose dependent. In contrast, type B reactions, which account for about 15% of ADRs, are traditionally regarded as unpredictable, dose-independent, idiosyncratic reactions.[9,10]

Skin rash is one of the frequently occurring ADRs. However, unlike isolated skin rash, Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug-induced hypersensitivity syndrome (DIHS), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis are life-threatening severe cutaneous adverse reactions (SCARs) accompanied by fever and systemic complications. SJS and TEN, with characteristic mucosal and cutaneous lesions, are now considered to represent different poles of the same reaction spectrum. SJS is defined as skin detachment involving <10% of the body surface, SJS/TEN overlap as skin detachment affecting 10%–30% of the body surface, whereas TEN as skin detachment involving >30%of the body surface.[11] TEN carries a mortality risk of 30%. The incidence of these SCARs is estimated to be 2–3 cases per million per year, but can vary with ethnicity.[12] Pathologically, SJS/TEN is considered to be delayed-type allergic reaction involving T cells. However, recent reports have implicated not only immunological but also genetic factors (HLA class I molecules) in the pathogenesis of CADRs. Box 5.2 enumerates some common drugs implicated in SCARs.

Box 5.2: Common drugs causing SCARs

- **Antiepileptic agents:**
  Carbamazepine (CBZ)
  Phenytoin
  Lamotrigine
  Zonisamide
- **Antibiotics:**
  Penicillin
  Cephalosporin
- **Anti-HIV agents:**
  Abacavir
  Nevirapine
- **Carbonic anhydrase inhibitors:**
  Acetazolamide
  Methazolamide
- **Nonsteroidal anti-inflammatory drugs (NSAIDs):**
  Diclofenac, Celecoxib
- **Urate-lowering agent:**
  Allopurinol
- **Organic solvent:**
  Trichloroethylene

PHARMACOGENOMIC APPROACHES USED TO IDENTIFY ASSOCIATED GENES

Candidate Gene Approach

It involves identifying association between various allelic variants or SNPs with the candidate gene and drug response.

Procedure:

- Selecting candidate genes based on disease pathophysiology, protein partners, or pathway members.

- Analyzing candidate gene by sequencing or SNP arrays.

  The advantage of the process is that it is less expensive. However, spurious association occurs if cases and controls are not well matched. Variants in other genes, which are remotely influencing drug response, cannot be identified and knowledge of the drug response pathway is required.

Microarrays (DNA Chip Technology)

By this process, simultaneous assessment of multiple genes can be done. Up to 64,000 gene clones can be evaluated on a single 1×1-inch slide.

Procedure:

- mRNA of interest is labeled with fluorochrome and then positive association between fluorescence intensity emitting from each gene clone and gene expression is observed.

  The advantage is that prescreening patients for polymorphisms before initiating therapy can be done.

Genome-Wide Association Studies

This approach is used in genetics research to look for associations between large numbers (typically hundreds of thousands) of specific genetic variations (most commonly SNPs) and particular diseases.[13] It is a very extensive and elaborate method to study various allelic variants occurring throughout the genome. This approach uses an SNP map.

The advantages are that genome-wide association studies (GWAS) can identify polygenic determinants of drug response and does not require prior information about drug response pathway like candidate gene approach. However, it is expensive.

Haplotype Analysis

It involves the study of clusters of SNPs occurring in the region with linkage disequilibrium in a chromosome and their association with drug response. Linkage disequilibrium is a condition where some specific variants of SNP markers, which happen to be close to that allele, are inherited together. The entire genome is not searched unlike in a genome-wide scan; only selected haplotypes are searched.

Bioinformatics

Here, the large amount of data generated in gene expression studies and genotyping is assimilated into software. Computer databases are created and then mined for genomic information. Computational and statistical algorithms are used for data mining to unearth significant associations. Large amount of information can be processed relatively easily if efficient algorithms are developed.

HUMAN LEUCOCYTE ANTIGEN (HLA) AND CADRS

HLA presents an antigen to the T-cell receptor, thereby initiating the T-cell-mediated immune response.[14] HLA alleles and ADRs are strongly associated, with the offending drug playing the role of the antigen. As supportive evidence, drug-specific $CD8^+$ cytotoxic cells activated in HLA class I–restricted pathway have been found in the blister fluid of SJS/TEN patients.[15] Presently, there are two drug presentation hypotheses: the hapten concept and the p-i concept.

The Hapten Concept

Covalent binding of a chemically reactive drug or metabolite to a protein or peptide gives rise to neoepitopes, which is presented by HLA.[16] Classical processing pathway then triggers T-cell activation and precipitates the adverse reaction. Examples are penicillin allergy and abacavir-induced hypersensitivity syndrome. Penicillin binds covalently with the lysine residue of the serum albumin to elicit penicillin allergy.[17]

The p-i Concept

This concept proposes direct interaction of the drug with immune receptors such as T-cell receptor or HLA. For example, CBZ directly reacts with HLA-B*1502, which activates the cytotoxic T-cell immune response. Noncovalent interacting forces (hydrogen bonds) and steric complementarity are responsible for this direct interaction.[18,19]

Type B ADRs, primarily SJS/TEN, drug hypersensitivity syndrome (DHS), have been found to be associated with HLA system. Drug hypersensitivity is mediated by adaptive immunity, which involves major histocompatibility complex (MHC)–restricted drug presentation, activation and clonal expansion of T cells. The specific MHC molecules involved have been identified; for example, HLA-B*5701 in abacavir-induced drug hypersensitivity and HLA-B*1502 in antiepileptic CBZ-induced SJS.

The association between HLA and ADR is phenotype specific. For example, with reference to CBZ-induced cutaneous ADRs, Han Chinese studies demonstrated that CBZ–SJS/TEN is highly associated with HLA-B*1502, whereas CBZ-induced maculopapular eruptions and DHS are not. Instead, CBZ-induced maculopapular eruption was found to be associated with SNPs in the HLA-E region and HLA-A*3101, and DHS with the MHC class II genes.[20]

Genetic association can show ethnic specificity related to differences in the allele frequency. In Japanese and Caucasian populations, HLA-B*1502 allele is low to absent; thus the susceptibility of CBZ–SJS/TEN is not associated with HLA-B*1502. Instead, CBZ–SJS/TEN is associated with HLA-A*3101, which is present with higher frequency in Japanese (9.1%) and Caucasians (5%) unlike Han Chinese (1.8%). Likewise, ethnic differences have been seen in genetic association of abacavir-induced hypersensitivity and the HLA-B*5701 allele, which is prevalent in Caucasians and Africans but is rare in Asians.[21,22] Thus, ancestry may play an important role in the biomarker assessment of ADRs.

A single HLA type has been found to be associated with CADRs in different populations. Allopurinol, a urate-lowering drug, frequently causes SJS/TEN, and the HLA-B*5801 allele is implicated. A strong association exists between HLA-B*5801 and Han Chinese patients living in Taiwan.[23] This association is also present in Asian and European patients. HLA-B*5801 is involved in the development of various types of SCARs both in Japanese[24] and in Korean[25] patients. A GWAS in Japanese patients detected SNPs on chromosome 6 that linked with HLA-B*5801.[26] This is as an inexpensive and simple screening test for HLA-B*5801, which uses one of the SNPs (rs9263726).[27] HLA-B*5801 is not only a risk factor for severe cutaneous reactions, such as SJS/TEN and DHS, but is also implicated in milder cutaneous adverse reactions, such as maculopapular erythroderma, in the Han Chinese population.[28]

Nevirapine, a potent nonnucleoside reverse transcriptase inhibitor used for the treatment of HIV-1 infections, frequently causes various types of skin rashes. HLA-B*35:05 allele is a strong predictor for nevirapine-induced skin reactions in HIV-infected Thai patients.[29] Korean and Japanese populations have shown predisposition toward SJS/TEN with carbonic anhydrase inhibitors, methazolamide and acetazolamide. The HLA-B59 serotype/HLA-B*59:01 has been reported to be associated with methazolamide- or acetazolamide-induced SJS/TEN.[30,31] This allele is infrequent in Caucasians and Africans.[22] An industrial solvent, trichloroethylene, has caused SCARs in industrial workers. An association between trichloroethylene-induced hypersensitivity and HLA-B*13:01 has also been reported in Chinese population.[32]

The HLA association with drug-induced hypersensitivity is stronger for certain drugs (OR > 100), which has been summarized in Table 5.1. There is a need to develop affordable tests to identify at-risk patients and prevent life-threatening CADRs. Wider availability of these tests can make personalized medicine a reality in everyday clinical practice.

Table 5.1: CADR associated with HLA with their odd ratio in different ethnic population

Drug	HLA allele	ADR	Ethnicity	OR
Allopurinol	HLA-B*5801	SCAR	HanChinese Japanese European Thai Koreans	580 41 80 348.3 97.8
CBZ	HLA-B*1502	SJS/TEN	HanChinese Indians Thai	2504 71.4 57.8
	HLA-A*3101	Maculopapular erythroderma SCAR CADR SJS SJS	HanChinese Japanese North Europeans Europeans Koreans	17 11 9 25.9 6.5
	HLA-B*1511	SJS/TEN SJS	Japanese Koreans	16.3 18.4
Lamotrigine	HLA-B*3801	SJS/TEN	European	32
Nevirapine	HLA-B*1505	CADRs	Thai	18.9
Abacavir	HLA-B*5701	Hypersensitivity syndrome	Western Australians Caucasians Africans	117 1945 900
Methazolamide	HLA-B*5901	SJS/TEN	Korean	250
Oxicams	HLA-B*7301	SJS/TEN	European	152
Phenytoin	HLA-B*1502	SJS/TEN	Thai	36
Sulfamethoxazole	HLA-B*3802	SJS/TEN	European	76
Trichloroethylene	HLA-B*1301	SCAR	Chinese in mainland	27.5

Adapted from Kaniwa and Saito[12] and Wei et al.[33]

BRINGING PHARMACOGENOMICS INTO CLINICS: SCREENING FOR CADR GENETIC BIOMARKERS

The association between CADRs and drugs is highly probable based on OR, and tests have been developed for well-defined genetic variants. Some of these tests have high positive and/or negative predictive values and may be used to guide drug selection and dose adjustment in high-risk populations. Examples of commercially available tests are given in Table 5.2. However, these tests are not yet generally available in India.

Table 5.2: Pharmacogenomic markers in predicting adverse reactions

Drug	Genetic marker	Clinical application
Carbamazepine Phenytoin	HLA-B*1502	Avoid usage in HLA-B*1502 carriers to prevent SJS/TEN
Allopurinol	HLA-B*5801	Avoid usage in HLA-B*5801 carriers to prevent severe cutaneous ADRs

In December 2007, Taiwan was the first country to include a warning in the package inserts of CBZ products that HLA-B*1502 is a risk factor for CBZ-induced SJS/TEN. PREDICT-I study was conducted on 2000 HIV-infected patients of Australia and Europe to evaluate the effectiveness of screening for HLA-B*5701 to prevent abacavir-induced hypersensitivity syndrome.[34] It was found that the occurrence of hypersensitivity was significantly lower in patients who received prospective screening. Currently, before initiation of abacavir treatment, prescreening for HLA-B*5701 is recommended in the United States and mandatory in the European Union.

CHALLENGES AND FUTURE SCOPE

The field of pharmacogenomics is by no means simple. Gene expression profiles of the blister fluid cells from SJS/TEN patients revealed more than 200 differentially expressed genes. Any or a combination of these genetic variations could contribute to the pathogenesis, clinical manifestations, and outcomes of the clinical syndrome.

The greatest hindrance to the clinical implementation of genetic biomarker tests is that, with the exception of those listed in Table 5.1, very few of them have satisfactory sensitivity, specificity, and predictive values to be clinically useful as screening tools to prevent CADRs. GWAS can identify multiple loci; however, each locus plays only a small role. The reason might be that the causes of common diseases are multifactorial, involving both genetic and environmental factors. Drug–drug or drug–diet interactions influence the response to many drugs. Evidently, more research is needed. Comprehensive studies using gene sequencing, GWAS, other approaches to identifying suspect loci, as well as epigenetics, proteomics, metabolomics, and environmental factor analysis approaches might reveal functional variants of responses to established and new drugs.

Sample size is an important consideration in genetic association studies. However, achieving an adequate sample size is much easier said than done because the incidence of severe ADRs is low, particularly for drugs that are less commonly used. Collaborative studies with similar and multiethnic populations are needed to address this issue. Finally, In-Silico approaches[35] would be valuable for predicting interactions between drugs and genes and their functional outcome. In-silico methods are of great value in target identification and in prediction of novel drugs. During the process of selection of novel drug candidates many essential steps are taken to eliminate compounds that have side effects and high potential for interaction with other drugs. In-silico drug designing software play an important role to design innovative proteins or drugs in biotechnology or the pharmaceutical field. The drug designing software and programs are used to examine molecular modelling of gene, gene expression, gene sequence analysis and 3D structure of proteins.[36]

LEARNING ESSENTIALS

- Genetic factors predispose to certain types of cutaneous reactions.
- Pharmacogenetics/pharmacogenomics principles aim to achieve optimal patient therapy and ensure drug safety based on their genetic makeup.
- A role of HLA gene as genomic biomarkers in predicting ADRs is being explored.
- The HLA associations have been found to have both phenotypic and ethnic specificity.
- A very strong association between CBZ-induced SJS/TEN and HLA-B*1502 has been observed in Han Chinese but not in Europeans.
- Similarly, HLA-B*5701 has been associated with abacavir hypersensitivity in several ethnic groups.
- Pre-prescription genotyping for HLA-B* 1502 and HLA-B* 5701 before administration of CBZ and abacavir has been advocated in some population groups to prevent occurrence of serious ADRs and has proved to be an effective and cost-cutting strategy in the management of drug reactions.

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Chapter

6

Scoring Systems in Cutaneous Adverse Drug Reactions

Akhilesh Shukla • Paschal D'souza

SUMMARY

Scoring systems in drug reactions are a useful tool to enable dermatologist arrive at a logical conclusion with regard to drug causality assessment, labeling a drug rash, knowing its severity, and predicting the outcome among other things. A number of scoring systems are available for causality assessment with different degrees of complexity which can be applied to all forms of cutaneous adverse drug reactions (CADRs), whereas the scoring systems for diagnosis are fewer and are specific to morphological drug patterns. Attempt has also been made to measure quality of life following CADR and predict the risk of CADR in elderly population who have multiple comorbidities and are on several drugs. Scoring systems assume great significance in the era of polypharmacy and consumer litigation. It can also guide physicians to adopt appropriate treatment protocols. Proper recording of CADRs in a uniform manner will help build worldwide data and strengthen pharmacovigilance.

INTRODUCTION

Cutaneous adverse drug reactions (CADRs) are defined as noxious, unintended, morphological skin changes, with or without systemic involvement, which develop after local or systemic administration of drugs in dosages commonly used for prevention, diagnosis, or treatment of diseases or modification of physiological functions.[1–3]

A number of scoring systems have been formulated by different authors to help assess different aspects of drug reaction, namely to implicate a particular drug in a particular reaction, to diagnose a particular morphological pattern of CADR, to assess the severity of an eruption, to prognosticate on outcome, to determine whether the CADR was preventable in the first place, and to predict risk of CADR in particular settings. The chapter provides an overview of the different scoring systems available, their strengths and weaknesses, and a proposal in certain cases to have a better system in place subject to validation in clinical situations.

CLASSIFICATION OF SCORING SYSTEMS

The classification of various scoring systems (Table 6.1), can be done according to their intended uses:

1. Scores for causality assessment
2. Scores for diagnostic purposes
3. Scores for severity assessment
4. Scores for prognosis
5. Scores for preventability
6. Scores for assessing risk of adverse drug reactions (ADRs)

SCORES FOR CAUSALITY ASSESSMENT OF CUTANEOUS ADVERSE DRUG REACTION

Many researchers developed various methods of causality assessment of ADRs by using different criteria such as chronological relationship between the administration of the drug and the occurrence of the ADR, screening for nondrug-related causes, confirmation of the reaction by in vivo or in vitro tests, and previous information on similar events attributed to the suspect drug or to its therapeutic class, to define ADRs in different categories.[4] But because there are no defined diagnostic criteria or categories, inter- and intrarater variabilities can be large.[5]

Table 6.1: Various scoring systems in cutaneous adverse drug reactions

Scores for	Name of scoring system
Causality	• Naranjo adverse drug reaction probability scale • WHO-UMC causality assessment • ALDEN • Kramer's algorithm • Dangaumou's French method • RUCAM algorithm • Korean algorithm, version 2.0
Diagnosis	• The RegiSCAR-Group Diagnosis Score for DRESS • Japanese group consensus for diagnoses of DIHS • EuroSCAR study group validation score for diagnosis of AGEP
Severity	• Grading system for scoring of anaphylactoid reactions • Modified Hartwig and Siegel severity assessment scale • DLQI
Prognosis	• SCORTEN • DAS-STOP • Auxiliary score
Preventability	• Schumock and Thornton scale
Assessing risk of ADRs	• GerontoNet ADR risk score

RUCAM - Roussel Uclaf Causality Assessment Method; WHO-UMC - World Health Organization–Uppsala Monitoring Centre; ALDEN - algorithm of drug causality for epidermal necrolysis; RegiSCAR - a multinational collaborative research team for study of severe cutaneous adverse reactions to drugs (SCAR); DRESS - drug reaction with eosinophilia and systemic symptoms; DIHS - drug-induced hypersensitivity syndrome; AGEO - acute generalized exanthematous pustulosis; DLQI - disability life quality index; SCORTEN - score of toxic epidermal necrosis; DAS-STOP - D'Souza and Shukla–SJS/TEN outcome probability; ADR - adverse drug reaction.

Naranjo Adverse Drug Reaction Probability Scale

The Naranjo algorithm, which was established in 1981, is the most widely used assessment tool and consists of 10 simple questions.[6] The merits of the Naranjo algorithm are that it is easy to apply, and assessment is possible with very little information and knowledge.[6] The downside of the Naranjo algorithm is the absence of a time-related detailed description (question 2), assessment for the response after administering a placebo that actually had not been carried out (question 6), and a nonconcrete question (question 10), which may cause differences between investigators.[6–8] In fact, there was much difference between the researchers in studies undertaken to determine the causality assessment for ADRs of inpatients (Table 6.2).[9,10]

Table 6.2: Naranjo adverse drug reaction probability scale

Question	Yes	No	Do not know	Score
1. Are there previous *conclusive* reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	−1	0	
3. Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0	
4. Did the adverse event reappear when the drug was re-administered?	+2	−1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2	0	
6. Did the reaction reappear when a placebo was given?	−1	+1	0	
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
Total Score:				

- Definite: Score ≥9
- Probable: 5–8
- Possible: 1–4
- Doubtful: ≤0

WHO-UMC Causality Assessment Criteria

WHO-UMC system has been developed in consultation with the National Centers participating in the Programme for International Drug Monitoring and is meant as a practical tool for the assessment of case reports.[11] It is basically a combined assessment taking into account the clinical–pharmacological aspects of the case history and the quality of the documentation of the observation. Since pharmacovigilance is particularly concerned with the detection of unknown and unexpected adverse reactions, other criteria such as previous knowledge and statistical chance play a less prominent role in the system. This method gives guidance to the general arguments that should be used to select one category over another.

WHO-UMC causality assessment method includes the following four criteria[12]:

1. Time relationships between the drug use and the adverse event.
2. Absence of other competing causes (medications, disease process itself).
3. Response to drug withdrawal or dose reduction (dechallenge).
4. Response to drug readministration (rechallenge).

The level of causal association is grouped into six categories, which are based on a number of the aforementioned criteria being met. Causal category is "certain" when all the four criteria are met. It is "probable" when criteria 1), 2), and 3) are met. When only criterion 1) is met, the event is categorized as "possible" and it is "unlikely" when criteria 1) and 2) are not met (Table 6.3).

Table 6.3: WHO-UMC causality assessment method

Categories	Time sequence	Other drugs/ disease ruled out	Dechallenge	Rechallenge
Certain	Yes	Yes	Yes	Yes
Probable	Yes	Yes	Yes	No
Possible	Yes	No	No	No
Unlikely	No	No	No	No

Source: Rehan et al.[12]

WHO-UMC - World Health Organization–Uppsala Monitoring Centre.

Beside these four categories, ADRs can also be categorized as "Unclassified/Conditional" or "Unassessable/Unclassifiable" in WHO-UMC causality assessment. The term "Unclassified/Conditional" is applied when more data are needed and such data are being sought or are already under examination. Finally when the information in a report is incomplete or contradictory and cannot be complemented or verified, the verdict is "Unclassifiable".

Dechallenge is the clinical decision to withdraw/discontinue a drug treatment after possible ADR has occurred. A dechallenge is "positive" or "suggestive" if the reaction abates, partially or completely when the drug is withdrawn, and it is considered to be "negative" or "against" if the reaction does not abate when the treatment is stopped.

Rechallenge is nothing but the deliberate or inadvertent administration of a further dose(s) of the same medicinal product to a person who has previously experienced an adverse event/ADR that might be drug related.

Failure of the product, when reintroduced, to produce signs and symptoms similar to those observed when the suspect drug was previously introduced implies a negative rechallenge, whereas recurrence of similar signs and symptoms on reintroduction of the suspect product implies a positive rechallenge.[13]

Algorithm of Drug Causality for Epidermal Necrolysis

Although rare, Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) remain of high interest in the field of drug safety and risk–benefit ratio evaluation of medicines because of their severity: The death rate from TEN averages 23%.[14] Therefore, a proper identification of the drug responsible for the disease is essential, not only for sponsoring and regulatory agencies but also for the purposes of adequate in vitro investigations into the mechanisms involved.

Algorithm of drug causality for epidermal necrolysis (ALDEN) score has the following six criteria for assessing the causality[15] (Table 6.4):

1. Delay from initial drug component intake to onset of reaction (index day)
2. Drug present in the body on index day
3. Prechallenge/rechallenge
4. Dechallenge
5. Type of drug (notoriety)
6. Others

Final score ranges from −12 to 10 and the causality is assessed as <0, very unlikely; 0–1, unlikely; 2–3, possible; 4–5, probable; and ≥6, very probable.

Table 6.4: Algorithm of drug causality for epidermal necrolysis

Criterion	Values	Rules to apply
Delay from initial drug component intake to onset of reaction (index day)	Suggestive +3	From 5 to 28 days
	Compatible +2	From 29 to 56 days
	Likely +1	From 1 to 4 days
	Unlikely −1	>56 days
	Excluded −3	Drug started on or after the index day
	In case of previous reaction to the same drug, only changes for Suggestive: +3, from 1 to 4 days; Likely: +1, from 5 to 56 days	
Drug present in the body on index day	Definite 0	Drug continued up to index day or stopped at a time point less than five times the elimination half-life before the index day.
	Doubtful −1	Drug stopped at a time point before the index day by more than five times the elimination half-life, but liver or kidney function alterations or suspected drug interactions are present.
	Excluded −3	Drug stopped at a time point before the index day by more than five times the elimination half-life, without liver or kidney function alterations or suspected drug interactions.
Prechallenge/ rechallenge	Positive specific for disease and drug: 4	SJS/TEN after use of same drug.
	Positive specific for disease or drug: 2	SJS/TEN after use of similar drug or other reaction with same drug.
	Positive unspecific: 1	Other reaction after use of similar drug.
	Not done/unknown: 0	No known previous exposure to this drug.
	Negative −2	Exposure to this drug without any reaction (before or after reaction).
Dechallenge	Neutral 0	Drug stopped (or unknown).
	Negative −2	Drug continued without harm.
Type of drug (notoriety)	Strongly associated 3	Drug of the "high-risk" list according to previous case–control studies.
	Associated 2	Drug with definite but lower risk according to previous case–control studies.
	Suspected 1	Several previous reports, ambiguous epidemiology results (drug "under surveillance").
	Unknown 0	All other drugs including newly released ones.
	Not suspected −1	No evidence of association from previous epidemiology study with sufficient number of exposed controls.
	Intermediate score = total of all previous criteria −11 to 10	
Other cause	Possible −1	Rank all drugs from highest to lowest intermediate score.
		If at least one has an intermediate score >3, subtract 1 point from the score of each of the other drugs taken by the patient (another cause is more likely).

SJS - Stevens–Johnson syndrome; TEN - toxic epidermal necrolysis.

Kramer's Algorithm

This algorithm applies to a single clinical manifestation occurring after administration of a single suspect drug. In cases where multiple drugs are involved, each is assessed separately. One of the advantages of this algorithm is its transparency. However, certain levels of expertise, experience, and time are required to use this method effectively.

Kramer's algorithm scores the ADRs from −7 to +7 based on the information for the previous experience, alternative explanation, timing of events, drug levels, dechallenge, and rechallenge[16] (Table 6.5).

Dangaumou's French Method

This method has been used by the French regulatory agency since 1977. The method separates an intrinsic

Table 6.5: Kramer's algorithm for adverse drug reaction

		Scoring of evidence for reaction		
Axis		**Favors**	**Uncertain**	**Against**
I	Previous experience	+1	0	−1
II	No alternative illnesses*	+2	0	−1
III	Timing of events	+1	0	−2
IV	Drug levels	+1	0	−1
V	Dechallenge	+1	0	−1
VI	Rechallenge	+1	0	−1
Total score		+7	0	−7

* No other illnesses explaining the presence of clinical manifestation in the patient.

As per this score, ADR is considered as "definite" (6–7), "probable" (4–5), "possible" (0–3), or "unlikely."

imputability (possible cause between drug and clinical event) from an extrinsic imputability (bibliographical data) using seven criteria (three chronological and four semiological) in two different tables.[17]

The chronological criteria are (i) drug challenge; (ii) dechallenge; and (iii) rechallenge, with an overall score of four possible categories.

The semiological criteria are (i) semiology (clinical signs) per se (suggestive or other); (ii) favoring factor; (iii) alternative nondrug-related explanation (none or possible); and (iv) specific laboratory test with three possible outcomes (positive, negative, or no test for the event–drug pair).

Scores are grouped into "likely," "possible," and "dubious." The advantage of this method is that it allows certain drugs taken at the same time with the "suspect" drug to be excluded, because each drug is imputed separately.

However, this method requires more time than most other algorithms.

Roussel Uclaf Causality Assessment Method

This method is designed for predetermined disease states such as liver and dermatological injuries.[4] Although this method seems quite easy to use, it is organ specific. Therefore, the criteria need to be defined by a consensus of experts for each medical field and validated before it can be of any meaningful use in ADRs other than hepatic or dermatological injuries (Table 6.6).

Table 6.6: Domains and weightings in Roussel Uclaf causality assessment method

Domains and weightings
1. Time to onset (0 to 2)
2. Course (−2 to 3)
3. Risk factors (age, alcohol, pregnancy) (0 to 2)
4. Concomitant drug(s) (0 to −3)
5. Exclusion of other causes of liver injury (−3 to 2)
6. Previous information on hepatotoxicity of the drug (0 to 2)
7. Response to readministration (−2 to 3)

Description of individual domain is beyond the scope of this chapter and authors recommend the readers to go through the reference.

Range of scores possible: −8 to 14

- Highly probable: >8
- Probable: 6–8
- Possible: 3–5
- Unlikely: 1–2
- Excluded: ≤0

Korean Algorithm (Version 2.0)

Hong et al.[7] developed the Korean algorithm and improved ambiguous descriptions of the clinical course in comparison to the Naranjo algorithm by adding proportional dose-dependent responses, event abatement, and clinical appearance on drug removal.[7,8,18] Some questions were specialized for consistent assessment as the period between administration and symptom onset, risk factors, and drug-unrelated factors.[7]

The items included in the Korean Algorithm are as follows:

1. Chronological relationship
2. Dose reduction or stopping of drug
3. Past history of ADR
4. Combined medication
5. Drug-unrelated cause
6. Any unveiled information of drugs (in label, insert, case reports etc.)
7. Rechallenge
8. Specific provocation tests, plasma drug level monitoring

SCORES FOR DIAGNOSTIC ASSESSMENT OF CUTANEOUS ADVERSE DRUG REACTION

RegiSCAR-Group Diagnosis Score

The RegiSCAR-Group has elaborated a scoring system for the diagnosis of DRESS (drug reaction with eosinophilia and systemic symptoms).[19]
This score is presented in Table 6.7.

Table 6.7: The RegiSCAR-Group diagnosis score for DRESS

Parameters	No	Yes	Unknown
Fever (≥38.5°C)	−1	0	−1
Enlarged lymph nodes (≥2 sites, >1 cm)	0	1	0
Atypical lymphocytes	0	1	0
Eosinophilia			
700–1499 or 10%–19.9%	0	1	0
≥1500 or ≥20%		2	
Skin rash			
Extent >50%	0	1	0
At least two of edema, infiltration, purpura, scaling	−1	1	0
Biopsy suggesting DRESS	−1	0	0
Internal organ involved			
One		1	
Two or more		2	
Resolution in >15 days	−1	0	−1
At least three biological investigations done and negative to exclude alternative diagnoses	0	1	0
Final score: <2, no case; 2–3, possible case; 4–5, probable case; >5, definite case			

DRESS - drug reaction with eosinophilia and systemic symptoms.

The scoring system mentioned in Table 6.7 is very holistic and includes all the important parameters affected in DRESS, but inclusion of biopsy findings, resolution after 15 days does not help to use the score during acute presentation of the patient.

Japanese Group Consensus

Japanese consensus group has given diagnostic criteria for drug-induced hypersensitivity syndrome (DIHS)[20] (Table 6.8).

The diagnosis is confirmed by the presence of all seven criteria (typical DIHS) or the presence of five criteria (atypical DIHS).

Table 6.8: Diagnostic criteria for DIHS established by the Japanese group

1. Maculopapular rash developing >3 weeks after starting with a limited number of drugs
2. Prolonged clinical symptoms 2 weeks after discontinuation of the causative drug
3. Fever >38°C
4. Liver abnormalities (alanine aminotransferase >100 U/L)
5. Leukocyte abnormalities (at least one present): • Leukocytosis (>11–109 per liter) • Atypical lymphocytosis (>5%) • Eosinophilia (>1.5–109 per liter)
6. Lymphadenopathy
7. Human herpesvirus 6 reactivation

DIHS - drug-induced hypersensitivity syndrome.

Validation Scoring System of the EuroSCAR Study Group for Acute Generalized Exanthematous Pustulosis

EuroSCAR study group has given a validation scoring system (Table 6.9)[21] for acute generalized exanthematous pustulosis (AGEP) according to the following:

- Morphology
- Histology
- Course

SCORES FOR SEVERITY ASSESSMENT OF CUTANEOUS ADVERSE DRUG REACTION

Grading System for Scoring of Anaphylactoid Reactions

Ring and Messmer described a grading system (Table 6.10) for severity assessment of anaphylactoid reactions.[22]

The advantage of this grading system is that it includes symptomatology of all the systems primarily affected in anaphylactoid reactions.

Modified Hartwig and Siegel Severity Assessment Scale

Severity of the reaction is assessed by using the modified Hartwig and Siegel severity assessment scale[23] and the severity is broadly categorized into "mild", "moderate", and "severe" for each ADR:

Table 6.9: AGEP validation score of the EuroSCAR study group

Variable	Score
Morphology	
Pustules	
Typical	2
Compatible	1
Insufficient	0
Erythema	
Typical	2
Compatible	1
Insufficient	0
Distribution/pattern	
Typical	2
Compatible	1
Insufficient	0
Postpustular desquamation	
Yes	1
No/insufficient	0
Course	
Mucosal involvement	
Yes	−2
No	0
Acute onset (≤10 day)	
Yes	0
No	−2
Resolution (≤15 days)	
Yes	0
No	−4
Fever (>38°C)	
Yes	1
No	0
PMN (>7000 per mm^3)	
Yes	1
No	0
Histology	
Other disease	−10
Not representative/no histology	0
Exocytosis of PMN	1
Subcorneal and/or intraepidermal nonspongiform with papillary edema or subcorneal and/or intraepidermal spongiform without papillary edema, not otherwise specified	2
Spongiform subcorneal and/or intraepidermal pustule(s) with papillary edema	3

Interpretation:

- 0: No AGEP
- 1–4: Possible
- 5–7: Probable
- 8–12: Definite

PMN, polymorphonuclear neutrophils.

Table 6.10: Grading system for scoring of anaphylactoid reactions

Grade	Symptoms			
	Skin	Abdomen	Respiratory Tract	Circulation
I	Pruritus, flush, urticaria, angioedema			
II	Pruritus, flush, urticaria, angioedema (not obligatory)	Nausea, cramping	Rhinorrhea, hoarseness, dyspnea	Tachycardia, hypotension, arrhythmia
III	Pruritus, flush, urticaria, angioedema (not obligatory)	Vomiting, defecation, diarrhea	Laryngeal edema, bronchospasm, cyanosis	Shock
IV	Pruritus, flush, urticaria, angioedema (not obligatory)	Vomiting, defecation, diarrhea	Respiratory arrest	Circulatory arrest

- The suspected ADR is "mild" when "an ADR occurs but requires no change in treatment with the suspected drug" or the ADR requires that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment requirement was required. No increase in length of stay (LOS).
- The suspected ADR is "moderate" when "the ADR requires treatment with the suspected drug be held, discontinued, or otherwise changed" and/or "an antidote or other treatment was required. No increase in LOS" or "any level 3 ADR that increases LOS by at least 1 day," or "the ADR was the reason for the admission."
- The suspected ADR is "severe" when "any level 4 ADR that requires intensive medical care or the adverse reaction caused permanent harm to the patient or the adverse reaction either directly or indirectly led to death of the patient."

Disability Life Quality Index

Many dermatological conditions frequently have a major impact on patient's psychological state, social relationship, and everyday activities.[24,25] Disability life quality index (DLQI) scale was developed to assess the impact of skin conditions on patient's psychological state and everyday activities.[26] Measure of DLQI scale in ACDR helps to assist treatment decisions as well as to guide priority of health services among different social and cultural groups.[27]

In an Indian study by Chaudhary Raju et al.,[28] the DLQI was calculated in patients of CADRs by summing up score of each question resulting maximum of 30 and minimum of 0. The score was compiled and the impact of ACDR according to meaning of DLQI score was concluded.

Meaning of DLQI scores

- 0–1: No effect
- 2–5: Small effect
- 6–10: Moderate effect
- 11–20: Very large effect
- 21–30: Extremely large effect

The domains assessed by DLQI were as follows:

1. Psychosocial items (Q-2, 5, 6, 8, 9)
2. Physical activities items (Q-3, 4, 7)
3. Symptoms items (Q-1, 10)[29]

Psychological items

Q-2: Embarrassed or self-conscious

Q-5: Effect on social or leisure activities

Q-6: Effect on sport activities

Q-8: Problem with partner, close friends, or relatives

Q-9: Difficulty in sexual activities

Physical activities items

Q-3: Interfered with shopping, looking after home, or gardening

Q-4: Effect on wearing clothes

Q-7: Prevented from working or studying

Symptoms items

Q-1: Itchy, redness, rawness, scarring, swelling, bleeding, sore, painful, or stinging

Q-10:Problem facing because of treatment

Authors created three types of scores using these three groups of questions. Psychosocial score was derived by adding scores of Q-2, 5, 6, 8, and 9; activity score was derived by summing up of scores of Q-3, 4, and 7; and symptoms score was derived by summing up of Q-1 and 10.

Total DLQI scores, independent of age, were higher for mean patients with exfoliative dermatitis (29), DRESS (28.5), and SJS (27); and was lowest for patients with lichenoid eruption (14) followed by fixed drug reactions (FDRs) (16.67).[28] It suggested exfoliative dermatitis, DRESS, and SJS pattern of ACDR had maximum impairment of quality of life as compared to others ACDR.

The DLQI scales assist in informing treatment decisions by identifying impact of different skin conditions. It also guides for providing priorities for services among different social and cultural groups.[27]

SCORES FOR PROGNOSIS OF ADVERSE CUTANEOUS DRUG REACTION

SCORTEN Score

A score termed as SCORTEN (Score of Toxic Epidermal Necrosis) was developed by Bastuji-Garin et al. in year 2000, as a severity-of-illness score for TEN.[30]

It is a validated predictor of mortality in patients with TEN when seen at the time of admission. The score is calculated by giving 1 point for each of the following 7 clinical variables during the first 24 hours of evaluation (Table 6.11).

Table 6.11: SCORTEN score for SJS/TEN[30]

- Age more than 40 years
- Malignancy
- Heart rate >120 beats per minute
- Initial epidermal detachment >10% of BSA
- Serum urea level >28 mg/dL (40 mg/dL in Indian settings)
- Serum glucose levels >250 mg/dL
- Serum bicarbonate levels <20 mEq/dL

SCORTEN - score of toxic epidermal necrosis; SJS - Stevens–Johnson syndrome; TEN - toxic epidermal necrolysis; BSA - body surface area.

The probability of death predicted by this score is as follows: 0–1 points: 0.03; 2 points: 0.12; 3 points: 0.35; 4 points: 0.58; and 5–7 points: 0.90. A probability of 0.90 means approximate 90 of 100 patients with TEN are expected to die. SCORTEN has been used extensively in a large number of studies with good to excellent accuracy in predicting death of cases with TEN.

However, Vaishampayan et al. conducted a prospective study to analyze efficacy of "SCORTEN" in 10 patients of SJS/TEN to predict mortality during their management.[31] Authors observed that if patients are analyzed with SCORTEN on a daily/alternate day basis, it will serve as a better predictor of mortality. They concluded that body surface area (BSA) involvement and age probably need more weightage in calculations, and besides malignancy,

tuberculosis and preexisting diabetes also need to be included while predicting mortality.

After going through the aforementioned study and our own experience in managing patients of SJS/TEN, we would like to propose the following score for predicting the mortality in patients of SJS/TEN.

D'Souza and Shukla–SJS/TEN Outcome Probability Score

The parameters proposed to be included with their respective scores mentioned ahead of them are shown in Table 6.12. This may take into consideration variables including history/presence of tuberculosis and other chronic illnesses that are important in a developing country like ours. In addition, as septicemia and acute respiratory distress syndrome (ARDS)/pulmonary edema are important causes of mortality in SJS/TEN, evidence of these conditions are included in the scoring system to make it more meaningful.

Table 6.12: DAS-STOP score for outcome probability in SJS/TEN

CHVariable	Score
1. Age	
More than 40 years	1
More than 60 years	2
2. History of tuberculosis sequelae/active tuberculosis infection	1
3. Known case of diabetes mellitus	1
4. Known case of HIV/immunocompromised state	1
5. Any other chronic illness	1
6. Heart rate > 120 per minute	2
7. Oral temperature (<95°F, >100.4°F)	2
8. BSA involved	
>10% and <30%	1
>30%	2
9. Urine output < 50 mL/hour	1
10. Hyperglycemia (>250 mg/dL) or glycosuria	1
11. Leukopenia or thrombocytopenia	2
12. Serum urea level >28 mg/dL	1
13. Hyponatremia or hyperkalemia	1
14. Serum bicarbonate levels <20 mEq/dL	1
15. Evidence of pulmonary edema	2
Total score: 0–21	

DAS-STOP - D'Souza and Shukla–SJS/TEN Outcome Probability Score; BSA - body surface area.

The outcome according to DAS-STOP score is graded as follows:

- 0–2: Good
- 3–5: Fair
- 6–10: Poor
- 11 and more: Guarded

We propose that this score should be calculated on alternate-day basis till the patient is admitted, which will not only help in further management but also help the physician know if the patient is responding to his/her treatment though the score needs to be validated through studies by different centers.

Auxiliary Scores

The auxiliary score is a simplified SCORTEN, which is easier to calculate and may be more appropriate in retrospective settings in the absence of laboratory data. In the absence of data to qualify scoring systems such as SCORTEN, auxiliary score (Table 6.13) can be used as a tool for calculating expected mortality.[32]

Table 6.13: Auxiliary score for SJS/TEN

Variable	Weight
Age 31–55 years	1
Age 56–75 years	2
Age >75 years	3
TEN (involved BSA >30%)	1
Presence of cancer or malignancy	1
Range of score	1–5

TEN - toxic epidermal necrolysis; BSA - body surface area.

Prediction of expected mortality is based on the following formula: exp (logit)/(1 + exp (logit)), where logit = –3.1364 + 0.9129 × auxiliary score value.[33]

SCORE FOR PREVENTABILITY ASSESSMENT OF A DRUG REACTION

Schumock and Thornton Scale

Schumock and Thornton scale is based on questionnaires.[34]

ADR is considered as "definitely preventable," if one or more of the following is present:

- History of allergy or previous reactions to the drug, inappropriate selection of drug in relation to diagnosis and characteristics of the patient.
- Documentation of toxic serum drug concentration (or laboratory monitoring test).
- Presence of a known treatment for the ADR.

ADR is considered "probably preventable", if one or more of the following is present:

- Lack of the required therapeutic drug monitoring or other necessary laboratory tests.
- Involvement of drug interaction; involvement of poor compliance.
- Lack of preventive measures causing reaction.

Otherwise ADR is considered as a "not preventable".

If we interpret the Schumock and Thornton scale of preventability in the Indian setup, inappropriate prescribing, medication errors, self-medication, over the counter (OTC) use, and ignoring history of allergy or CADRs may be responsible factors.[35]

SCORE FOR ASSESSING RISK OF ADVERSE DRUG REACTIONS

GerontoNet Adverse Drug Reaction Risk Score

Older patients are particularly vulnerable to drug-related illnesses because they are usually on multiple drug regimens, which expose them to the risk of drug interactions,[36] and because age is associated with changes in pharmacokinetics and pharmacodynamics.[37] To assess the risk of ADR in elderly population (≥65 years) GerontoNet ADR risk score (Table 6.14) was evaluated by Onder et al. [38]

A score of ≥8 increased the risk of developing ADR by 21.7%. Awareness of this risk in the elderly will enable doctors to keep a close watch on the possibility of patient developing a cutaneous eruption so that appropriate treatment can be instituted early.

Table 6.14: GerontoNet ADR risk score

Variable	Points
≥4 Comorbid conditions	1
Heart failure	1
Liver disease	1
No. of drugs	
≤5	0
5–7	1
≥8	4
Previous ADR	2
Renal failure*	1

* Defined as a glomerular filtration rate of less than 60 mL/minute.

LEARNING ESSENTIALS

- Knowing and using different scoring systems in CADR will help to assess causality of drugs, establish diagnosis of drug eruption particularly SCARS, know the severity of the rash and its prognosis, and find out whether the particular CADR was preventable in the first place.
- These scores can also predict the risk of developing CADR in certain populations such as the elderly.
- The documentation of patients with CADR in this way would also help in comparing data being generated from different parts of the world and strengthen pharmacovigilance ultimately benefitting both dermatologists and patients.
- However, an ideal, simple, uniform, easy-to-use and reproducible scoring system for different aspects of CADR is yet to be developed and newer scoring systems need to be developed and constantly validated in clinical situations.

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Chapter

7

Approach to a Suspected Drug Reaction

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SUMMARY

Cutaneous adverse drug reactions (CADRs) are an ever-increasing cause of morbidity and mortality among dermatology patients. They need to be factored in as a differential diagnosis in both typical and atypical dermatoses. Early diagnosis of a cutaneous rash as being drug induced ensures prompt withdrawal of the drug and prevents further progression. The diagnosis of CADR is often based on clinical judgment, because definitive, confirmatory drug-specific testing is difficult and of low reliability. The probability that a drug has caused a clinical outcome can be assessed by considering certain features of the drug in relation to the adverse reaction. These include, among others, the dose and duration of drug, temporal correlation between administration of drug and occurrence of eruption, and assessment of a patient's susceptibility factors. Most combine five criteria, challenge, dechallenge, rechallenge, previous description in the medical literature, and elimination of other possible causes/confounders, to arrive at a diagnosis of cutaneous drug eruption. An ideal approach to a patient with suspected CADR would be to think of it in the first place on the basis of a good history and workup followed by assessing the severity, identifying the offending agent, instituting appropriate management measures, recording and reporting it to appropriate authorities, and taking prophylactic steps to prevent its recurrence.

INTRODUCTION

Adverse drug reactions (ADRs) are one of the major preventable public health problems. They are common but are underreported and underrecognized cause of morbidity and mortality. Every clinician involved in patient care is likely to encounter ADRs in their clinical practice at some point of time. Skin is the commonest and most easily observed target organ that is affected by a drug reaction. Any inflammatory or noninflammatory dermatosis can virtually be mimicked. Thus the aphorism-"Anything you see, anything you think of and something that you don't even think of, could be due to drugs!!"

Presentation of cutaneous drug eruptions can range from an asymptomatic rash to a life-threatening emergency. Fortunately, most reactions are benign and do not cause significant complications and sequelae. However, a few reactions such as toxic epidermal necrolysis (TEN), Stevens–Johnson syndrome (SJS), drug hypersensitivity syndrome (DHS), erythroderma, and vasculitis may have serious consequences. Because of the morbidity and potential mortality associated with drug eruptions, it is important to be able to promptly recognize, work up, and treat patients with possible drug reactions.[1]

CUTANEOUS ADVERSE DRUG REACTION: A PRACTICAL APPROACH

As presentations of drug reactions can be confusing at times, a methodical approach needs to be adopted. This is especially so in a busy practice scenario. The physician/dermatologist must be able to–

1. Recognize an eruption as drug induced.
2. Manage the drug reaction in its active stage.
3. Manage complications and sequelae of the reaction.
4. Identify host factors including immunosuppression and genetic predisposition.
5. Prevent further recurrence of a subsequent episode.

Recognizing a Drug Eruption

> Medicine is a science of uncertainty and art of probability.
>
> **—William Osler**

A strong clinical suspicion backed up by a rich experience is often required to pick up a drug rash. A thorough and meticulous history including all medications taken by the patient, their dose and duration of intake, temporal correlation between the introduction of drug and appearance of rash, and history of similar reactions are essential in the "history checklist" for diagnosis. A family history of similar reactions should raise the possibility of heritable metabolic derangements (pharmacogenomics in drug reactions).

In practice, the diagnosis of a cutaneous drug eruption begins with the right clinical judgment of morphology of the rash. Certain morphologies such as SJS, TEN, acute generalized exanthematous pustulosis (AGEP), and fixed drug eruption have distinctive presentations, which prompt a clinician to initiate a drug enquiry. However, certain others such as urticaria and anaphylaxis, blistering disorders, and erythroderma are presentations wherein drug is only one of the several etiologic factors. An even higher index of suspicion will be required when one encounters rashes that are aggravations of common dermatoses like eczematous dermatitis, psoriasiform lesions, lichenoid morphology, acneiform eruptions, pigmentary changes, hair loss, and nail abnormalities. Potentially serious drug eruptions are likely to be picked up earlier than the smouldering ones.

Laboratory confirmation of a drug reaction is largely supportive and not absolute in relevance. Routine screening may reveal eosinophilia, leukocytosis, and raised erythrocyte sedimentation rate (ESR), which serve as pointers toward a drug reaction. Derangement of hepatic enzymes and renal parameters and elevation of blood sugars suggest systemic involvement. A skin histology helps in differentiating drug reaction from other mimics but is not conclusive. It acts as a corroborative evidence only. As there are no reliable and confirmatory in vivo or in vitro laboratory tests, the diagnosis largely depends on the clinician's acumen and judgment.

It should be remembered that every rash that develops in a patient on medication does not necessarily imply that it is drug related. Other possibilities should be kept in mind while making a diagnosis, as the management plan will depend on the cause of the rash. For example, differential diagnosis for an exanthematous drug eruption may include viral exanthems, bacterial infections, collagen vascular disease, and neoplasia.[2] Box 7.1 outlines the general criteria for the diagnosis of a drug-induced eruption.

Box 7.1: General criteria for diagnosis of cutaneous adverse drug reaction

- The patient's symptomatology is consistent with a drug reaction.
- The patient was administered a drug known to cause such symptoms.
- The temporal sequence of drug administration and appearance of symptoms are consistent with a drug reaction.
- Other causes of the symptomatology are effectively excluded.
- Laboratory data are supportive of an immunologic mechanism to explain the drug reaction (not present or available in all cases).

Source: From Riedl and Casillas.[2]

Recognizing Risk Factors in a Patient with Suspected Cutaneous Adverse Drug Reaction

If a patient has a known risk factor for an association between the suspected drug and an adverse event, a causative association is more likely. Various risk factors associated with drug reaction are mentioned in Box 7.2.

Box 7.2: Factors influencing the risk of drug reactions

- Elderly[3,4]
- Boys <3 years, girls older >9 years[5] and female gender.[4,6,7]
- Viral infections—cytomegalovirus (CMV), Epstein–Barr virus (EBV), HIV[8]
- Systemic connective tissue disease[8]
- Oncologic disease and immunosuppressed states
- Impaired hepatic/renal function
- Polypharmacy[9]
- Drug–drug interactions[10]
- Food–drug interactions
- Genetic variations—e.g. slow and fast acetylators, glucose-6-phosphate dehydrogenase (G6PD) deficiency[11]
- Human leukocyte antigen (HLA) grouping [e.g. HLA-DR4 and drug-induced pemphigus, HLA-B7 and insulin allergy,[12,13] HLA-B22 and fixed drug eruption (FDE)][14]
- Atopic patients[15]

Source: From Riedl and Casillas.[2]

Sometimes, the chemical properties and molecular weight of the drug could be the risk factor. The drug with high molecular weight and greater structural

complexity (e.g. nonhuman proteins) are more likely to be immunogenic and a cause of cutaneous adverse drug reaction (CADR). Heterologous antisera, streptokinase, and insulin are examples of complex antigens capable of eliciting hypersensitivity reactions. Most drugs have a smaller molecular weight (less than 1000 daltons), but may still become immunogenic by coupling with carrier proteins, such as albumin, to form simple chemical–carrier complexes (hapten).[2]

Recognizing the Pattern of Drug Eruption

CADR, as mentioned earlier, can cause a variety of skin lesions and morphological patterns, thus mimicking any inflammatory dermatoses. Exanthematous rash, fixed drug reaction, and urticaria are the commonly reported reaction patterns in most studies. Recognizing morphological patterns may offer a clue to acuteness of the condition (e.g. SJS/TEN), the possible pathogenetic mechanism involved (e.g. urticaria and anaphylaxis are often type 1 hypersensitivity), the likelihood of systemic involvement [e.g. maculopapular rash with facial edema indicates a drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome], and the drugs commonly implicated in a particular CADR.

Proper documentation and photography, wherever feasible, are essential for diagnosis, for tracking the evolution of the rash, and for streamlining treatment decisions. They may also serve as evidence in legal and ethical discussions.

Table 7.1 lists the common drug reaction patterns with their salient clinical features, time of onset in relation to drug exposure, and common offending drug(s).

Table 7.1: Characteristics of major cutaneous drug eruption

Type of eruption	Morphology	Mucous membrane involvement	Time of onset	Commonly implicated drugs
Exanthematous	Erythematous Generalized No blistering	Absent	4–14 days	Antibiotics, antiepileptics, allopurinol, nonsteroidal anti-inflammatory drugs (NSAIDs)
Fixed drug eruption	One or more round, well circumscribed, erythematous, edematous plaques Sometimes central bullae	Present	First exposure: 1–2 weeks Re-exposure: <48 hours, usually within 24 hours	Cotrimoxazole (trimethoprim/sulfamethoxazole) NSAIDs Tetracyclines Pseudoephedrine
Urticaria	Wheals Pruritus	Absent	Minutes to hours	Penicillins Opioids Aspirin/NSAIDs Sulfonamides Radiocontrast media
Angioedema	Swollen deep dermal and subcutaneous tissue	Present or absent	Minutes to hours	Angiotensin-converting-enzyme (ACE) inhibitors Aspirin/NSAIDs
Acneiform	Inflammatory lesions No comedones Atypical sites	Absent	Variable	Iodides Isoniazid Corticosteroids Androgens Lithium Phenytoin
Lichenoid eruption	Pruritic, flat-topped, violaceous papules and plaques	Rare	1 month to 2 years	Gold, NSAIDs, ACE inhibitors, antimicrobials, and antiarthritics
Psoriasiform drug reaction	Limited or generalized erythematous plaques with thick, large, silvery scales, pustular lesions, or erythroderma	Absent	Weeks to years	β-blockers, lithium, synthetic antimalarials, NSAIDs, and tetracyclines
Pityriasis rosea	Fewer, larger, bright violet-to-red macules, patches, and plaques with scaling across the entire lesion. No herald patch	Can be present	1–2 weeks	ACE inhibitors, NSAIDs, clozapine, anti-tumor necrosis factor (TNF)-α inhibitors, and breakpoint cluster region- Abelson (BCR-ABL) tyrosine kinase selective inhibitors

(Continued...)

Table 7.1: Characteristics of major cutaneous drug eruption (Continued)

Type of eruption	Morphology	Mucous membrane involvement	Time of onset	Commonly implicated drugs
Erythroderma	Erythematous and pruritic patches involving >90% of the cutaneous surface	Absent	2 weeks to several months	β-blockers, trimethoprim, sulfamethoxazole, ketoconazole, griseofulvin, nifedipine
Acute generalized exanthematous pustulosis	Nonfollicular, sterile pustules, arising on background of edematous erythema	Present or absent	<4 days	β-lactam antibiotics Macrolides Calcium channel blockers
Drug-induced hypersensitivity syndrome	Severe exanthematous rash	Infrequent	1–6 weeks	Anticonvulsants Sulfonamides Allopurinol
SJS	Atypical targets <10% body surface area	Present	7–21 days	Anticonvulsants Sulfonamides Allopurinol NSAIDs
TEN	Confluent and extensive epidermal detachment >30% body surface area	Present	7–21 days	Anticonvulsants Sulfonamides Allopurinol NSAIDs

Recognizing Severity of Drug Eruption

The next step in evaluating a potential drug reaction is to assess the severity. The severity assessment is important to guide the therapy and to assess the prognosis.

Four categories of eruptions, based on the primary lesion- exanthematous, urticarial, blistering and pustular, are potentially serious and life threatening. These may or may not be accompanied by extracutaneous signs (e.g. malaise, fever, hypotension, tachycardia, lymphadenoapathy, synovitis, and dyspnea). It is important to realize that a rash may initially appear benign but may later develop into a serious rash. The classical example is that of TEN and DHS/DRESS, which may evolve from a simple maculopapular rash. Cutaneous features along with the presence of these extra cutaneous signs may aid in distinguishing benign cutaneous drug eruption from potentially severe systemic drug eruptions (Box 7.3).[16]

Therefore, while assessing the severity, clinicians should be alert to recognize these warning signs, which could indicate serious multisystem involvement. They point toward a serious cutaneous adverse reaction (SCAR) and require hospitalization of the patient and an aggressive management.

An approach to determine the severity of a CADR is summarized in a flow chart in Fig. 7.1.

Box 7.3: Clinical pointers that indicate a serious drug reaction

Cutaneous/mucocutaneous

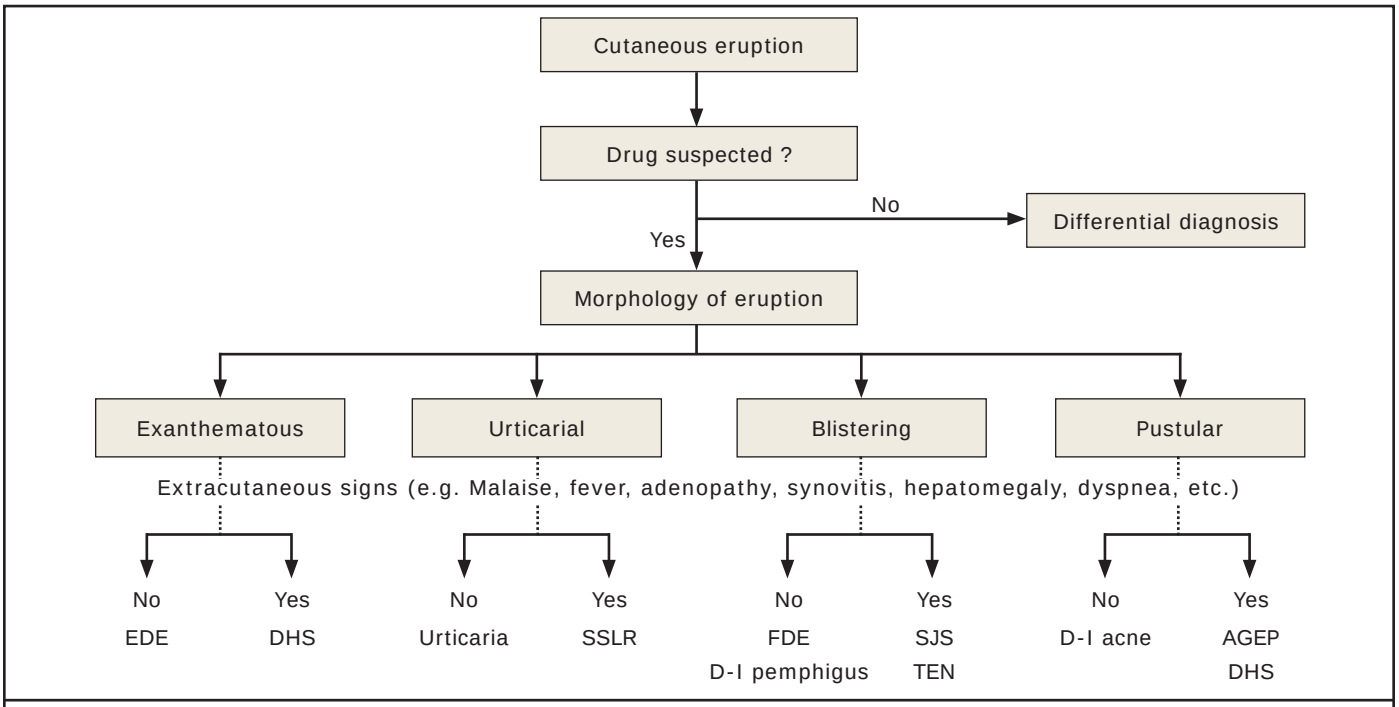
- Extensive cutaneous involvement (75%), erythroderma
- Widespread bullae and skin detachment
- Skin tenderness, centrofacial edema
- Purpura
- Skin necrosis
- Atypical target lesion
- Erosions of mucosa (≥2)

Extracutaneous

- Fever >38.5°C, pharyngitis, dysphagia/dyspnea
- Lymphadenopathy
- Hepatosplenomegaly
- Anxious/toxic look of patient
- Hematological alteration (neutropenia, anemia, thrombocytopenia, eosinophilia, atypical lymphocytes)
- Impaired hepatic and/or renal functions

Recognizing Drug Exposure/Reaction Pattern and Detecting Offending Drug

Identification of culprit drug(s) and avoiding their use in future are the most effective preventive measures against another episode(s) of ADR. This is easy when a single drug has been taken by the patient. In most cases, however, the patient is on multiple drugs at the time of drug eruption.



EDE - Exanthematous drug eruption, DHS - Drug hypersensitivity syndrome, SSLR - Serum sickness like reaction, FDE - Fixed drug eruption, D-I - Drug induced, SJS - Steven Johnson syndrome, TEN - Toxic epidermal necrolysis, AGEP - Acute generalized exanthematous pustulosis.

Source: Nigen et al.[16]

Fig. 7.1: Algorithm to aid the initial diagnosis of a cutaneous reaction.

There are challenges to this investigative exercise in many developing countries like India, where self-medication is common and there are no strict regulations on purchase of over-the-counter medications. Patients, in many instances, are not provided with any medical prescription/records and practitioners simply dispense medicines without a formal prescription. Patients often do not preserve their treatment records. This makes it a daunting task for the dermatologist and the possibility of identifying the drug is missed out.

When nature of drug(s) is/are known, an appropriate method for drug exposure analysis is the creation of a "timeline" to facilitate assessment of the chronology of the events. Each drug, its dosage and duration, the date of initiation, its stoppage, the onset of rash, the progression of rash, and all pertinent signs and symptoms should be included on this timeline. This serves as a very useful tool to ascertain a causal association.

The initial history should ideally include a recording of all prescription and nonprescription drugs taken within the last 2 months, including dates of administration and dosage. All medications, regardless of route of administration, must be considered. Drugs taken intermittently or on an "as-needed" basis must be considered. History regarding dietary supplements, all vitamins, pain medications, sedatives, laxatives, oral contraceptives, over-the-counter medications, and natural products and alternative medications should be taken. The patients should be questioned regarding the temporal relationship between drug intake and the onset of clinical symptoms. The latent period between drug intake and development of rash is significantly shorter if the patient is previously sensitized than during the first exposure to the drug. A history of reaction in the past with the same or structurally related drug is very helpful in ascertaining the drug-related nature of rash. A history of reaction in family members particularly to anticonvulsants should also be recorded. Drug interactions should also be noted, because these can sometimes precipitate a drug rash. Algorithms are available that deal with causality assessment in a particular CADR and can be used by the physician to help him arrive at a proper conclusion.

Identifying the offending agent is necessary for other reasons too. A patient wrongly diagnosed to have an ADR, or wherein a wrong drug has been identified as the culprit, stands at a risk of losing out on a vital drug, especially in emergency or life-threatening situations e.g. an antibiotic of choice in a septicemia patient. Also when allergies are not documented in all further prescriptions, the patient is likely to be administered the drug inadvertently.

A detailed drug evaluation, recording of drug events, and documentation, accompanied by drug rechallenge by experts, with generation of a list of safe drugs for the patient, make medication administration a safe exercise. Drug rechallenge, however, in inexperienced hands could be an unsafe procedure in those individuals who have had life-threatening ADRs, especially SCAR.

Recognizing Offending Drug by Literature Search

A literature search provides information regarding the frequency with which the specific morphologic pattern may be related to a particular drug. The DERM index, PUBMED, Litt's DERM, and MEDLINE are useful references for the dermatologist. However, it is important to keep in mind that regardless of literature data, all drugs must be considered a possible cause of any reaction, even if a drug is not widely known to be associated with a particular reaction. Information on onset and duration of the reaction, effectiveness of diagnostic tests, such as skin testing, and use of alternative non-cross-reacting drugs may also be gleaned from this research.[16]

Recognizing CADR on the Basis of Laboratory Results and Diagnostic Tests

Like any other disease, several laboratory tests are available to evaluate and confirm the diagnosis of CADR, assess its severity, detect other organ/s involvement, identify offending drug in some cases, and exclude other possible causes of similar-looking cutaneous eruption. None of the tests, however, are specific and presently are at best supportive.

Blood Investigations

In some cases, these may be useful in aiding the clinical diagnosis. These include complete blood count (atypical lymphocytosis, neutrophilia, eosinophilia, etc.) and liver and renal function tests. Other blood tests [enzymes, electrolytes, biochemistry, ESR, antinuclear antibodies (ANA), bacterial and viral serology, etc.] can be requested depending on the suspected diagnosis. Culture (skin, blood, tissue, etc.) and medical imaging can also be done if appropriate, which may aid in confirming or ruling out potential differential diagnoses.[16]

When the usual target blood (whole blood, plasma, or serum) concentration range of the suspected drug is known, a concentration above that range increases the suspicion of a drug-induced cause.

The following tests help confirm specific conditions:

- Elevated serum tryptase concentration: anaphylactic reaction.
- Low C4 levels: Angioedema alone (no urticaria).
- Complete blood count (CBC): Normal in drug-induced lupus, in contrast to abnormal in systemic lupus erythematosus (SLE).
- Antibodies to single-stranded DNA/histone: Drug-induced lupus.
- Antibodies to double-stranded DNA: SLE.

Histopathological Examination

Cutaneous biopsies (histopathology and direct immunofluorescence) can sometimes distinguish between a drug induced and other diseases. For example, TEN can mimic a staphylococcal scalded skin syndrome, but a biopsy would differentiate between the two, particularly the frozen sections. Infiltration of eosinophilic polymorphonuclear leukocytes may suggest a drug-induced lesion. In DRESS, the most common finding on histologic examination is a dense, superficial perivascular lymphocytic infiltrate, spongiotic or lichenoid dermatitis, and variable degree of edema depending on the lesion biopsied. However, biopsies do not allow for identification of the causative drug.

In Vitro Tests

A list of in vitro test is given in Box 7.4.

Box 7.4: In vitro tests for CADR

- Histamine release test
- Basophil degranulation test
- Passive hemagglutination
- Leukocyte and macrophage migration inhibition factor tests
- Lymphocyte transformation test
- Lymphocyte toxicity assay

These tests are apparently safer than in vivo tests.[16] However, they are not freely available and practically are largely research tools at present. If at all they are used, results should be interpreted only in conjunction with patient history and clinical findings.

In Vivo Tests

In vivo tests include skin testing, dechallenge, and provocation or rechallenge test.

1. ***Prick and intradermal testing:*** They have been found to be useful for confirmation of IgE-mediated immediate hypersensitivity reactions. Unfortunately, skin testing has only been validated for a few drugs, such as penicillin.
2. ***Patch testing:*** Patch testing may be helpful to confirm allergic contact dermatitis, fixed drug

eruptions, exanthematous drug eruptions, DHS, AGEP, and other delayed skin eruptions, but no validated protocol has been established for these tests.[16] For example, if patch testing is to be performed in patients with a history of anticonvulsant hypersensitivity syndrome, 1% and 10% carbamazepine or phenytoin in petrolatum compound is recommended. In addition, at least 2 months should elapse from the eruption to the testing date since either false-positive reactions due to increased reactivity or false-negative reactions due to a refractory state may exist.[17]

3. ***Dechallenge and rechallenge:*** Dechallenge is improvement after a decrease in dosage or stopping of a suspected drug. Disappearance of the lesion after withdrawal of a suspected drug increases the probability of a causal association; failure to resolve after withdrawal is against the diagnosis. However, non-drug-induced skin lesions can resolve coincidentally after withdrawal of a drug, and drug-induced lesions can persist despite drug withdrawal due to long half-life of certain drugs and persistence of metabolites in the system. Lichenoid drug reaction is one such example where the eruption may take a long time to subside even after stoppage of suspected drug.

Rechallenge is recurrence or exacerbation of eruption after re-exposure to a drug. The provocation test can be performed unblinded or as double-blind, placebo-controlled procedure to avoid false-positive reactions.[16] For example, photoallergic contact dermatitis might be reproduced by applying the suspected drug to skin on one side of the body and a placebo on the other and exposing both areas to light. Recurrence of the lesion after rechallenge strongly suggests a drug-induced lesion. Oral rechallenge is time-consuming and generally avoided in cases of serious drug reactions. However, a view prevails that rechallenge or "supervised drug administration" can be and should be performed even in SCAR in an orderly, methodical, supervised way, not only to confirm offending drug but also to give a list of safe drugs that the patient can take if he or she develops similar or unrelated illness. This is deemed a much safer procedure when done in a supervised manner, in hospital settings, with the team of experts available to handle the emergency, if any, to a more risky option when the patient consumes the offending drug inadvertently.

Managing Established CADR

Once diagnosis of CADR is established and the offending drug identified, it is imperative to discontinue it immediately to prevent further progression of the CADR before other measures are taken. If the agent cannot be identified with certainty, then ideally all drugs being taken by the patient at that point of time should be withheld. This is easier said than done as some of the patients are on critical lifesaving drugs, the withdrawal of which could endanger their lives. In such a situation, the advice should be to withdraw all nonessential drugs and if possible substitute the essential drugs with alternate medications of different pharmacological groups having similar pharmacologic action and used for same indication.

In treating CADR, specially the severe ones, time is a crucial factor. Hence, it is essential to admit these patients in a well-equipped setup while immediately instituting supportive and specific measures. This is especially so in cases of CADRs such as angioedema, SJS/TEN, DHS/DRESS, and erythroderma. There are debatable issues with specific therapies such as systemic corticosteroids but all agree to the benefits of good basic supportive nursing care and multidisciplinary coordinated approach in many of the severe CADRs. Corticosteroids should, however, be instituted at an early stage and for fairly prolonged period in patients with DHS/DRESS. Here, it is pertinent to state the importance of accurate classification of CADR for therapeutic purpose. The aggressiveness of treatment has to be commensurate with the gravity of CADR. Misclassification may limit therapeutic options and can lead to the use of more-expensive drugs. For example, a rash in a patient with AGEP may look very threatening but does not require intensive treatment unlike a patient with SJS/TEN.

Reporting CADR to Appropriate Authorities

Recording and reporting of CADR has always been a weak link in the chain of measures to tackle the issue of ensuring future drug safety. This is because most CADRs are mild and tolerable and so are conveniently ignored both by patients and by physicians. This neglect may have a high price later, as reactions on re-exposure with the same drug can be severe and even deadly. We also have to contend with the fact that ADRs to new drugs may often be delayed because they have a long latency or are rare or unexpected. This means that these ADRs will be missed during phase II and III trials where duration of study period is short and will emerge only slowly after marketing. Awareness and proactive efforts by patients, physician, pharmaceutical industry, and regulatory authorities is therefore important to detect, record, and disseminate knowledge about ADRs and ensure drug safety. The importance of pharmacovigilance therefore cannot be overstated. Postmarketing surveillance networks, observational studies, and registries to identify adverse events are required if we want to have a safe pharmaceutical milieu for our patients.

Prevention of CADR

"Be safe than sorry" should be our guiding motto in the management of drug reactions. Situations involving higher risk for drug reactions need to be identified and preventive action need to be undertaken. It is necessary to assess risk based on the drug (e.g. phenytoin and carbamazepine have higher incidence of drug reactions in comparison to sodium valproate in epilepsy), disease (in EBV-associated infectious mononucleosis, ampicillin-associated rash should be anticipated), underlying comorbidity (in patients with renal dysfunction, gadolinium contrast media can cause scleromyxedema), race, or genetic makeup (e.g. abacavir in Africans and Europeans with HLA-B*5701, carbamazepine in Han Chinese and Indians with HLA-B*1502).

Extreme care should also be taken to treat patients or even relatives with past history of CADR, specially the severe ones. Patients with ADRs should be educated to always carry "drug alert card" with them whenever they need medical care and show it to their treating physician. Recent advances in rapid DNA sequence analysis have enabled discovery of genetic biomarkers of ADR susceptibility, which could be used in future for systematic testing of patients in order to optimize treatment decisions. Medical product labels describing caution for use in cases of polymorphisms of cytochrome P450 isoenzymes have come up in the West, advising testing to inform optimal dosing of the drug. With a high positive predictive value for immunologically confirmed hypersensitivity reactions in HLA-B*5701-positive patients, the Food and Drug Administration (FDA) has recommended screening patients for whom abacavir therapy is planned. Similarly, screening prior to carbamazepine therapy has been recommended by the FDA in most patients of Asian ancestry and has emerged as a cost-effective strategy in management of SCARs in countries like Taiwan.

CONCLUSION

A logical approach to a drug rash starting with correct diagnosis, based primarily on the dermatologist clinical acumen along with supportive historical evidence, will pay rich dividends. A timely assessment of severity and the correct classification of CADR will help prioritize management options. Identifying offending drug is one of the toughest part of the workup and requires a combination of meticulous history taking, applying standard available causality criteria, performing literature search, and undertaking certain supportive laboratory investigations and in vivo tests including dechallenge and rechallenge within appropriate timeline. Once the diagnosis of CADR has been established, most important part of the management includes immediate discontinuation of the offending/suspected drug(s) and instituting relevant supportive and specific therapeutic measures. Appropriate documentation and reporting of CADR to regulatory authorities to strengthen pharmacovigilance is an important but often neglected part of management protocol. The algorithm is incomplete without ensuring safe drug therapy for patients by preventing recurrence of CADR in those previously affected. Advancements in genetic testing to identify subsets of population susceptible to certain drugs so as not to expose them to further risks of CADR and thus reducing the morbidity burden due to this largely preventable condition may hold a promising future in effective management of CADRs.

LEARNING ESSENTIALS

Clinical Approach To A Suspected Drug Reaction

HISTORY CHECKLIST

- Review patient drug list
  - Prescription as well as nonprescription drugs
  - Vitamins, supplements, pain relievers, laxatives, oral contraceptives, and native and indigenous medications
- Create a drug and rash "timeline"
  - Drug related: Time of initiation, dose and duration administered, time of stoppage of drug

CLINICAL EXAMINATION CHECKLIST

- Prodromal symptoms: Malaise, fever, flu-like symptoms
- Morphology of rash-macular, papular, maculopapular, pustular, urticarial, vesiculobullous, pityriasiform, erythroderma, eczematous, purpuric
- Distribution of rash: Generalized, localized, flexural (e.g. SDRIFE)
- Pruritus: More often seen when the rash is drug related
- Mucosal involvement: Single/multiple mucosae
- Palms and soles involvement
- Hair and nail involvement
- Systemic signs: Gastrointestinal, respiratory, hepatic, pulmonary, neurologic

Lab evidences

Lab tests are often done to exclude other differentials. There are no specific tests that point to a drug reaction. Tests that raise a strong suspicion of a drug reaction include the following:

- Eosinophilia
- Leukocytosis
- Raised ESR
- Histopathology: eosinophilic response
- Anti-histone antibody in drug-induced lupus erythematosus (LE)
- In vitro and in vivo testing of suspected drugs

Causality assessment

- To be done by experts (dermatologist, clinical pharmacist, trained physician)
- Naranjo probability scale
- World Health Organization -Uppsala Monitoring Centre (WHO–UMC) scale

Drug withdrawal

Drug dechallenge, rechallenge (not to be done in severe ADRs-SCAR)

- Reporting to appropriate authorities

Rash related

Onset of rash, progression, associated signs and symptoms

- Identify temporal correlation between the introduction of drug and appearance of rash
- History of similar reactions in the past
- Family history of reactions to similar drugs
- Foods that may have precipitated the drug reactions

Pharmacovigilance

Literature search

- DERM index, PUBMED, Litt's DERM, and MEDLINE

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Chapter 8

Ensuring Drug Safety in Dermatology Practice: An Overview

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SUMMARY

Ensuring drug safety is of paramount importance to every clinician. Owing to the perceived benign nature of skin diseases, the harm resulting from medication is relatively less expected and accepted by the patients with dermatologic diseases. The adverse drug reactions (ADRs) are a major cause of morbidity and may cause significant mortality besides severely jeopardizing the "doctor–patient" relationship and culminating in litigations at times. Ensuring safety of drugs is not only the sole responsibility of prescriber but patient and drug manufacturers can also play an important role. The chapter briefly describes the role of stakeholders-physicians, patients, and drug manufacturers in maximizing the drug safety.

INTRODUCTION

Practicing medicine is not only science but an art as well. Health and diseases can be considered as the two sides of a coin. Though the drugs are used to alleviate the sufferings of ailing patients, they may sometimes act like a double-edged sword that may harm in the form of ADR. ADRs may be considered to be the inevitable price we pay for the benefits of modern drug therapy. These are costly in terms of the human illness caused and economic loss, and can undermine the doctor–patient relationship.[1] The World Health Organization has defined an ADR as "An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product".[2]

The ADRs may lead to one or more of these consequences viz. deterioration of the quality of life, interruption of the desired treatment, drug substitution with expensive alternative regimen, threat to life, and also possible medicolegal consequences. These events may be prevented to a large extent by adopting a cautious approach by both the clinician and the patient. This chapter briefly provides an overview on the practical approach to maximize and ensure drug safety in dermatology practice.

GOALS OF DRUG SAFETY

These are important to both patient and the prescriber and are as follows:

1. To ensure physician's ethical obligations
2. To maximize patient's medical outcome
3. To minimize medicolegal risks

RELEVANCE TO DERMATOLOGISTS

Although ensuring safety of drugs is of prime importance in all specialties, its relevance in dermatology is even more desirable and greater as these patients are comparatively less sick and do not usually require an aggressive therapy. They are therefore less likely to accept complications related to any aggressive therapy of a relatively benign underlying disease being treated. Napoleon Bonaparte said, "I do not want two diseases—one from the nature and the other from doctor".

STAKEHOLDERS IN DRUG SAFETY

1. Patients
2. Physicians
3. Drug manufacturers

Patient's Responsibility

Although ensuring the drug safety is expected primarily from the prescriber who is generally blamed for any ADR, the patient also has significant role to play. It is not uncommon on the part of patients to conceal vital details of their illness and concomitant alternative and complementary medications that they may be consuming. They often indulge in self-medication, obtain treatment from quacks or over-the-counter (OTC) products, and do not preserve or carry medical records. Therefore, the patients also need to be constantly counseled so as to make them realize their role in reducing the risk of ADRs. They need to be involved in their treatment plan and educated about the general aspects of ADRs as well as specific reaction to the medication they are being prescribed. Appendix 1 provides some basic information about ADRs of practical relevance to the patients. The patient's obligations to ensure the drug safety have been highlighted in Box 8.1 and Appendix 1.

Physician's Responsibility

The safety of patient is of prime importance and every clinician has an obligation to fulfill the Hippocratic admonition—"first of all be sure that you do no harm" (primum non nocere). Fact however remains that despite executing extreme caution, a physician may encounter ADRs. This is on account of the unpredictability of human body and its response to the administered drug (s). There exists no ideal drug that is completely devoid of adverse effects and no medical risk reduction system can be expected to be perfect. However, every clinician should aim to execute highest degree of caution while treating their patients and to be a safe physician. Box 8.2 highlights the various interdependent components (arranged in alphabetical order from A to M) of physician's responsibility to ensure drug safety.

Box 8.2: Physician's obligations in ensuring drug safety

- Anticipatory approach
- Baseline evaluation
- Counseling
- Documentation
- Evidence-based approach
- Futuristic approach
- Guidelines
- High-risk assessment
- Interactions
- Judgment
- Knowledge
- Learner's approach
- Management

Anticipatory Approach

A clinician should always be wary of the fact that every patient has the potential to develop a drug reaction anytime to any drug ("Any drug can cause any rash".—Litt's).[3] The clinician should, therefore, have a proactive approach in preempting and preventing such events from occurring.

Baseline Evaluation

Patient should be interrogated in detail about the intake of drug, both prescriptional as well as nonprescriptional, previous episode(s) of reaction to

Box 8.1: Instruction to the patients

- Avoid medications for minor ailments.
- Avoid self-medication, even the topical ones.
- Take medication under strict medical supervision only.
- Avoid seeking treatment from unqualified persons/quack.
- Do not increase the dose or duration of treatment on your own.
- Inform your physician about history of allergy to any drug in you or your family members.
- Do not panic. Report immediately to the physician in case of suspected event.
- Bring all medical documents along with unconsumed medications/wrapper/package etc. to help your doctor to identify the culprit drug.
- Carry the details of drug(s) causing reaction and show it to the treating doctor each time.
- Do not blame your doctor for reaction.

Table 8.1: Important baseline investigations

Corticosteroids	Complete blood count (CBC), blood sugar, chest X-ray, ECG, eye checkup, bone scan
Chloroquine	CBC, eye checkup
Methotrexate	CBC, renal function test (RFT), liver function test (LFT), chest X-ray
Cyclosporine	RFT, serum lipids
Retinoids	LFT, serum lipids
Dapsone	CBC, LFT, RFT, glucose-6-phosphate dehydrogenase (G6PD)
Tumor necrosis factor (TNF) inhibitors	Chest X-ray, Mantoux test and/or interferon gamma release assay (IGRA)
Thalidomide	Urine pregnancy test in females of reproductive age group before starting treatment and before issuing subsequent prescriptions (never prescribe more than 4 weeks supply at a time). Baseline nerve conduction study especially sensory nerve action potential.

drug(s) in patient as well as family members, and presence of comorbid conditions (immunosuppression, renal and/or hepatic dysfunction, etc.). Relevant baseline investigations should be undertaken before commencing therapy (Table 8.1). Many drugs require sensitivity testing before their administration. Testing for drug sensitivity should be carried out "every time" before such drug is administered (e.g. sensitivity testing to penicillin and local anesthetic agents). This is important as the person may develop adverse reaction during subsequent use of the same drug despite its safe use in the past.

Counseling

This is a very important aspect of prescribing drug and ensuring safety. Establishing a "therapeutic partnership" with a patient is helpful in allaying the patient's anxiety about the disease and also developing a mutual trust. It helps to ensure compliance and safety of therapy. Patient should be provided very clear and unambiguous written instructions regarding dose, frequency, and duration of medications (Box 8.3). Adherence to the treatment and a need for regular follow-up should be insisted. The patients should be explained about some of the adverse effects that normally occur in all patients during the therapy and they should not discontinue the therapy. The examples include cheilitis with oral retinoids and red discolored urine from rifampicin. They should be discouraged about self-medication and instructed not to extend or discontinue the therapy on their own as this may sometimes lead to disastrous consequences; the classical example being Addisonian crisis resulting from abrupt stoppage of prolonged intake of systemic corticosteroids. It should also be emphasized that even the topical therapy may lead to systemic complications viz. occurrence of cataract and glaucoma following periocular use of steroids and "hypothalamus–pituitary–adrenal axis suppression" with prolonged use of potent steroids. The patient should be advised to report immediately in case of any unexpected event following medications. Informed written consent should be obtained wherever applicable e.g.

Box 8.3: Patient counseling points in ADRs

- Develop a mutual trust and therapeutic alliance with the patient
- Obtain written consent for unconventional/risky therapy/procedure
- Provide clear, written instruction about nature, dose, frequency, and duration of therapy
- Ensure adherence and compliance
- Strictly instruct to avoid pregnancy during use of teratogenic, mutagenic, or high-risk drugs
- Warn on the consequences of prolonging therapy beyond prescribed limit or abrupt cessation
- Inform the patient about the warning signs of drug reaction
- Ask the patient to report immediately in case of any unexpected event
- Discourage telephonic consultations

before therapy with drugs such as oral retinoids, thalidomide, intravenous immunoglobulins, high-dose supra pharmacological pulse therapy with steroids, immunosuppressives, biologic agents, and targeted therapies. Special precautions to be undertaken by the patient should be clearly communicated e.g. sedation from antihistamines, wearing of protective eye wear, and shielding of genitals during phototherapy. Pregnancy and lactation status should always be enquired from female patients of reproductive age and therapy planned accordingly (for details, refer to chapter 45 on CADRs in pregnancy and lactation).

Documentation

The importance of maintaining and preserving the medical documents is often a neglected aspect both by the patients and by the clinicians and should not be underestimated. It helps to retrieve the medical details during subsequent visits, saves time, and aids in choosing the safer alternatives if the patient has history of ADRs to any agent. It is also a safeguard against possible medicolegal consequences. The episode of drug reaction should be documented clearly and legibly in the medical records. Baseline and serial photographic documentation should be done in patients with serious reactions such as Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). ADRs must be reported to the related drug regulatory authorities.

Evidence-Based Approach

In the present era of technique-savvy consumer and easy and rapid access to electronic communication, many patients are well informed about their disease and various treatment options and may question the therapeutic decision of their physician. A physician should therefore practice an evidence-based management approach as far as possible. "Evidence-based practice" is defined as integrating one's clinical expertise with the best external evidence from systemic research.[4] Use of unconventional and "off-label" medications should be avoided and the references be kept ready in case of their use. Simple and topical treatment should be tried first before resorting to potentially risky and systemic therapy in recalcitrant cases. It is better to err on a conservative side especially in children, elderly, and patients with hepatic or renal compromise rather than adopting an aggressive approach.

Futuristic Approach

The practitioner should adopt a futuristic approach and remain updated with the recently introduced medications and their potential toxicities. The details of banned drugs must be known and their use should be avoided.

Guidelines

The therapeutic guidelines keep changing. The new medications are constantly introduced in the market. The clinician should therefore remain updated with the latest guidelines on treatment of disease as well as drug reactions. Some of the useful guidelines on the subject include the British Society for Allergy and Clinical Immunology (BSACI) guidelines (2008) for the management of drug allergy,[5] the UK guidelines (2016) for the management of SJS/TEN,[6] the Indian guidelines (2016) for the management of SJS/TEN,[7] and the top 100 drug interactions 2016 guideline.[8]

High-Risk Assessment

The probability of developing reaction to drug(s) differs in an individual depending on several factors such as age, gender, nature of the drug, concomitant medications, genetic susceptibility of a person, and comorbid conditions. Some drugs are notorious ("red flag") to cause reactions and clinicians should exercise utmost care while using them or use a safer substitute instead. Being aware of the high-risk drugs (Box 8.4) and high-risk situations (Box 8.5) may help to prevent the drug reactions significantly.

Box 8.4: High-risk drugs for ADRs[1]

- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Sulfonamides
- Antibiotics
- Antiretroviral drugs
- Antitubercular drugs
- Antiepileptics
- Allopurinol
- Antihypertensives
- Antimalarial drugs

Interaction

The practice of polypharmacy is very prevalent. Sick patients and elderly are often on multiple medications and this increases the chances of drug interactions and drug reactions. Having a thorough knowledge about interactive potential of drug–drug, drug–food, and drug–herbs can help to prevent

Box 8.5: High-risk situations for ADRs

- Previous reaction(s)
- Elderly
- Polypharmacy
- Immunosuppression (100 times risk with sulfa drugs in AIDS patients)
- Collagen vascular diseases (Sjogren's syndrome, rheumatoid arthritis, systemic lupus erythematosus (SLE), etc.)
- Genetic predisposition [certain human leukocyte antigen (HLA) associations]
- Renal impairment
- Hepatic impairment

the complications resulting from coadministration of drugs. The drug interactions usually follow 80/20 rule, i.e. 80% interactions result from 20% drugs.[9] It is very helpful to be aware of this fact. A thorough knowledge of CYP-450 drug-metabolizing enzyme system and individual pharmacogenetic variation is important to understand drug interactions. Some of the examples of clinically important interactions relevant to dermatology practice include the following: Methotrexate with NSAIDs, sulfa drugs, and oral retinoids (increased risk of renal, hematological, and hepatotoxicity, respectively); azathioprine with allopurinol (increased hematological toxicity of azathioprine; febuxostat can be used safely with azathioprine); itraconazole with lovastatin or simvastatin (rhabdomyolysis; rosuvastatin and fluvastatin may be used safely); cyclosporine (CsA) and ketoconazole (enhanced CsA toxicity); and oral contraceptive pills (OCPs) with rifampicin or broad-spectrum antibiotics (failure of OCPs). For further details on drug interactions refer to chapter 46 on clinically important adverse drug interactions in dermatology.

Judgment

Clinical judgment whether the rash is due to the administered drug or exacerbation of primary disease or appearance of a new dermatosis is very important, though difficult. This is because the clinical spectrum of drug reactions is very wide and ADRs can practically mimic any inflammatory dermatosis. The latency between the initiation of drug and the appearance of rash is extremely variable and the rash may develop even after years of drug intake e.g. lichenoid drug eruptions and pseudolymphomatous drug reactions. Fatal angioedema to captopril has been reported after 2 years of its use.[10] The lack of substantiated and validated in vivo and in vitro laboratory methods further compounds the situation. The ascertainment of causality of drugs to the rash therefore remains a diagnostic and therapeutic dilemma, and the diagnosis is mainly based on the clinical expertise and judgment. A possibility that an initially benign-appearing rash may get converted into a serious reaction should always be kept in mind. For instance, TEN, erythroderma, and drug hypersensitivity syndrome (DHS) may initially begin as maculopapular rash before turning in to a more ominous rash. The clinician should be able to recognize the warning signs (Box 8.6). In the event of reaction, the judgment whether the ongoing treatment needs to be "carried through" or "abruptly stopped" is very relevant. In situations that require disruption of therapy, a decision on which drug to stop and which alternative substitute to use is very important.

Knowledge

> Knowledge is the most powerful medicine.
>
> ***—Socrates***

Knowledge tends to decay with time. Prescribers should therefore keep themselves abreast with the current knowledge about newer drugs, and their interactive and reaction potential. Common as well

Box 8.6: Warning signs of serious ADRs

- Mucocutaneous: Skin tenderness, centrofacial erythema and edema, atypical target lesions purpura, bullae, and widespread erosions
- Systemic: Anxiety, malaise, fever, lymphadenopathy, arthralgia/arthritis, jaundice
- Laboratory: Cytopenias, eosinophilia, impaired liver and renal function

as rare presentation of drug reactions with their management should be known.

Learner's Approach

One should always remember that howsoever cautious a clinician may be, there is always a chance of encountering ADRs. Therefore, they should always adopt a lifelong learners' approach in anticipating and managing ADRs. The clinician ought to consult the current literature, database, and other resources in the field of ADRs and remain constantly updated. Box 8.7 lists some of the useful websites and resources on the subject.

Management

The ideal management of ADR's is their prevention and early diagnosis. Every effort should therefore be made to minimize the chances of occurrence of ADRs. Some examples of such preventive strategy include avoidance of aspirin and angiotensin-converting enzyme (ACE) inhibitors in patients with urticaria/angioedema and asthma; chloroquine in patients with retinopathy; sulfonamides, sulfones, and chloroquine in patients deficient in G6PD enzyme. Care should be taken to avoid concomitant use of drugs with strong interactive potential. Toxicity of medications may sometimes be reduced or prevented by appropriate supplementation with other agents. Supplementation of folic acid may help to reduce the gastrointestinal and hematological toxicity of methotrexate. Likewise, supplementation of calcium, vitamin D_3, and bisphosphonates may help to reduce the osteoporosis resulting from prolonged use of systemic corticosteroids. At times, simple measures such as avoiding rapid infusion of drugs may help reduce chances of complications of therapy e.g. "red man syndrome" due to vancomycin. Temporary cessation of ongoing medication may help to reduce complications e.g. stopping aspirin or anticoagulant therapy before dermatosurgical procedure may reduce the risk of bleeding during and after the procedure.

The management plan in established ADR will depend on the nature of the reaction. In nonserious reactions such as benign maculopapular rash, a close observation while continuing the therapy i.e. a "carry through approach" can be adopted. Reduction in dose or temporary cessation of treatment may be necessary in some cases. However, in serious reactions where the culprit agent is not ascertained, the entire treatment must be stopped and the patient must be hospitalized. Supportive and specific treatments are instituted as per the nature and severity of the reaction. For the management of primary disease, culprit drug should be substituted with structurally and chemically unrelated agent.

For nonserious reactions, drug challenge may be undertaken after the recovery to ascertain the culprit drug and/or generate a list of safe as well as unsafe drugs. A clear written instruction in the form of card mentioning the details of suspected drug(s) should be issued to the patient. The patients are instructed to always carry this card and show to the treating physicians every time.

Role Of Drug Manufacturers

Physicians, regulatory/licensing agencies, and drug manufacturing units should work in tandem to protect public health and ensure drug safety. Premarketing surveys, done on a relatively smaller

Box 8.7: Useful resources/websites related to ADRs

- Cochrane Skin Group: http://www.csg.cochrane.org
- Cochrane Library: http://www.thecochranelibrary.org
- Litt's D.E.R.M.: www.drugeruptiondata.com
- The National Institute for Health and Clinical Excellence (NICE): www.nice.org.uk
- Meyler's Side Effects of Drugs: http://www.elsevier.com
- Reactions Weekly and Reaction Database-Adis Press: http://www.ovid.com
- Australian Adverse Drug Reaction Bulletin: http://www.tga.gov.au/adr/aadrb.htm
- MedWatch: http://www.fda.gov/medwatch/
- http://www.drugs.com
- http://www.medscape.com/druginfo/
- http://www.who.int/druginformation/
- http://www.cdsco.nic.in/

and healthy population, fail to detect the rare and serious ADRs with low incidence, which are reported only when the drug is used in larger number of patients. The drug manufacturers should collect, investigate, and proactively evaluate this information and adopt appropriate corrective measures in compliance with the regulatory agencies. Some of the measures to be ensured by manufactures include critically ensuring launch of safe products, developing greater "in-house" expertise, avoiding hiding or misrepresentation of clinical trial data, engaging in structured epidemiological research, and maintaining an internal, interdisciplinary senior level safety council.[11]

LEARNING ESSENTIALS

- ADRs to medications are common and at times inevitable; preventing them from occurring is the best management strategy.
- Ensuring drug safety is extremely important to optimize the patient therapy, fulfill the physicians' ethical obligations, and prevent any possible medicolegal complications.
- Though patient and the drug manufacturers have an important role, it is primarily physician's duty to exercise extreme caution in ensuring drug safety.
- Establishing a **"therapeutic partnership"** with the patient and counseling are strategically very important in optimizing therapy and ensuring safety.
- Anticipatory approach that "any drug can cause any rash any time in any person" should always be kept in mind.
- A proper evaluation including detailed history of reactions in the past, high-risk assessment, comorbidities, relevant laboratory investigations, and drug sensitivity testing wherever relevant should be carried out.
- As far as possible, "evidence-based practice" should be adopted. In children and elderly, topical and less aggressive treatment approach is helpful.
- Adopt a futuristic and lifelong learner approach keeping abreast with updated guidelines, database on ADRs, and drug interactions.
- Prompt diagnosis by recognizing the warning signs of drug reactions and abrupt stoppage of all suspected drugs in cases of serious reactions is most important aspect of management.
- A proper documentation of reactions including photodocumentation of serious drug reactions should be done in medical records.
- Patients must be warned not to consume the suspected drug(s) and issued a drug alert card with instructions to carry this all the times and to show it to the treating physician.

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Chapter

9

Intradermal Tests and Skin Prick Tests for the Diagnosis of Drug Allergy

Sushil Pande

SUMMARY

Intradermal tests (IDTs) are commonly used for detecting hypersensitivity to various infectious antigens. Its use in the detection of IgE-mediated immediate hypersensitivity reaction to drugs has also been popular, although limited by certain challenges. When foreign antigen like a drug is introduced in the skin by a prick or by intradermal injection, it leads to a wheal formation in already sensitized individual. Dermatologists are usually required to undertake these tests for drug-induced urticaria/angioedema syndromes. Before performing skin prick tests (SPT)/ IDTs, possibility of anaphylactic reaction during test procedure should be kept in mind and facilities for management of anaphylactic reactions must be made available. Similarly, before performing SPT/IDT, antihistamines, glucocorticosteroids, and beta blockers should be stopped for a suitable period of time as discussed in this chapter. It is recommended that SPT/IDT should be performed after 3 weeks following subsidence of a drug reaction and no later than 3 months. Adequate and nonirritant concentration of a test drug diluted with 0.9% NaCl is injected intradermally to look for "wheal" response as against positive and negative control. Sensitivity of SPT/IDT is moderate to high for immediate hypersensitivity reaction due to β-lactam antibiotics, perioperative anesthetic drugs, heparin, and radiocontrast dyes, whereas it is low for other drugs. SPT/IDT requires further standardization particularly with regard to test concentration of drugs. A clinical correlation and experience is needed to impart much needed validity and reliability to this diagnostic technique.

INTRODUCTION

Intradermal skin tests, in vivo laboratory tests, and provocative tests are diagnostic tests useful for the diagnosis of drug allergy. Of these, provocative tests could be potentially hazardous or harmful to the patient in the clinical practice. Laboratory tests for detection of drug-specific IgE antibodies are less sensitive than intradermal test and are available for a few select drugs.[1,2] Hence, intradermal tests (IDTs) and skin prick tests (SPTs) are commonly used for the diagnosis of detecting cutaneous hypersensitivity to drugs. IDT to detect IgE-mediated type I hypersensitivity reaction to penicillin or its components is a prototype example of this. In contrast to this, IDTs such as Mantoux test or tuberculin skin test (TST) are meant to detect type IV or delayed hypersensitivity reaction to mycobacterial antigens and T-lymphocytes play an important role in it. Many a times, IDTs are done to detect hypersensitivity to antigens produced by infectious agents.

In this chapter, role of IDTs and SPT is being discussed in the acute type of cutaneous drug reactions like drug-induced urticaria, angioedema, or anaphylaxis.

MECHANISM OF IDTS AND SPTS

In both IDT and SPT, allergen introduced in the dermis binds to IgE antibodies to cause mast cell degranulation and subsequent release of histamine from the mast cell. This happens if the skin is reactive or hypersensitive to a particular foreign antigen or a drug. Histamine being a vasodilator produces localized dermal edema and erythema to produce wheal at the injected or pricked skin site after 20 minutes. Although SPT and IDT have same immunologic basis, there are certain differences that are enlisted in Table 9.1.

INDICATIONS OF SPT/IDT

IDTs/SPTs are useful in IgE-mediated immediate

Table 9.1: Differences between skin prick test (SPT) and intradermal test (IDT)

SPT	IDT
Easy to perform	Less easy to perform
Multiple allergen can be tested in the same sitting	Testing multiple allergen is cumbersome and inconvenient to a patient.
Less painful	More painful
Relatively safe	Less safe than SPT
Less sensitive	More sensitive
Less chances of irritant or false-positive reaction	More chances or irritant or false-positive reaction

type of drug hypersensitivity reactions like urticaria/angioedema, anaphylaxis, bronchospasm, allergic rhinitis, and allergic conjunctivitis. Of these clinical indications, dermatologists are usually required to undertake these tests for urticaria/angioedema syndromes. IDTs are more popularly done for detecting hypersensitivity to β-lactam antibiotics. They have also been performed for detecting IgE-mediated reactions to heparin, protamine sulfate, insulin, muscle relaxants, streptokinase[3], iodinated radiocontrast dyes[4], estradiol[5], corticosteroids[6], diltiazem, metamizole, human papilloma virus vaccine containing polysorbate 80,[7] vancomycin[8], teicoplanin, rifampicin[9], etc. List of drugs for which value of skin tests has not been adequately established is given in Table 9.2.[2] Delayed or late positivity of IDT is also seen in drug-induced maculopapular rashes, fixed drug reaction, erythroderma, and eczema. Thus, IDT is useful for both IgE-mediated immediate hypersensitivity reaction and non-IgE-mediated cutaneous drug reactions as mentioned earlier. Sensitivity of SPT/IDT is moderate to high for immediate hypersensitivity reaction due to β-lactam antibiotics, perioperative anesthetic drugs, heparin, and radiocontrast dyes, whereas it is low for other drugs.[2]

Table 9.2: Drugs for which value of skin tests is not adequately established

- Antihypertensive drugs
- Biologicals other than omalizumab and tumor necrosis factor (TNF)-α inhibitors
- Hormones, corticosteroids, and insulin
- Non-β-lactam antibiotics
- Nonsteroidal anti-inflammatory drugs except pyrazolones
- Opioids
- Sera, immunoglobulins, and vaccines
- Non-platinum chemotherapeutic agents

Source: Brockow et al.[2]

PREREQUISITES FOR SPT/IPT

IDTs are usually recommended when the clinical symptoms have resolved and when drug concentration of offending medications has reduced in the blood and patient is not on any antiallergic medications. In resource-limited setup like India, it may not always be possible to detect blood levels. A list of antiallergic medications or medications that would alter vascular or systemic response includes mainly antihistamines, glucocorticosteroids, and beta blockers. Antihistamines, imipramines, phenothiazines, and beta blockers should be stopped at least for 5 days before undertaking SPT/IDT. Drug-free interval for short-acting glucocorticosteroids (prednisolone or prednisolone equivalent of less than 50 mg) and long-acting glucocorticosteroids should be 3 days and 3 weeks, respectively.[3]

Before performing SPT/IDT, possibility of anaphylactic reaction during test procedure should be kept in mind. Preferably, all SPT/IDT should be done in high-dependency units or intensive care units where facilities for emergency care and facilities for management of anaphylactic reactions are available.

It is recommended that SPT/IDT should be performed after 3 weeks following subsidence of a drug reaction and no later than 3 months.[3] However, information about sensitization level or immunologic status following drug reaction is not completely known.

PROCEDURE AND INTERPRETATION OF SPT/IDT

Both, IDT and SPT are easy-to-perform and easy-to-interpret skin tests. In SPT, allergen in the solution form is applied on the surface of the skin and a small prick is given in the skin where allergen is applied. This is done with the help of lancet or a needle to make a point break in the integrity of epidermis to allow entry of allergen in the superficial dermis. In IDT, a small amount of allergen i.e. 0.02–0.05 mL in the solution form is injected directly into the dermis of volar forearm with the help of a tuberculin syringe with needle or insulin syringe to raise a bleb of 3 mm diameter. A similar amount of normal saline is injected intradermally on other forearm as a negative control. For SPT, histamine solution (10 mg/mL) is used as a positive control.

SPT or IDT are read after 20 minutes for detection of immediate type of reactions. For detection of nonimmediate or late reactions, a reading is taken after 24 and 72 hours. If the mean wheal diameter is more than 3 mm (as compared to control) and is associated with flare after 15–20 minutes, it is considered as positive SPT/IDT test. Similarly, if histamine is used as positive control, then mean wheal diameter of more than or equal to histamine wheal is considered as positive. For late reactions, additional features like erythematous papules, vesiculation, or infiltrated erythema should be considered. Late reaction is seen especially with heparin i.e. at Day 3 as suggested by a few authors.

The SPT and IDT should be interpreted in the context of clinical scenario as many factors may influence the test results. These include the following:

Positive IDT

1. Patient has IgE-mediated immediate hypersensitivity ADR or has drug allergy.
2. False-positive or irritant reaction (when high concentration of a drug is used).

Negative IDT

1. Patient has no allergy to drug or drug reaction is due to nonallergic mechanism.
2. Inadequate test reagents, inadequate test concentration, or faulty testing procedures.
3. Missing concomitant factors required for a drug to become antigenic e.g. drug–virus interactions.
4. Drug produces given reaction by drug–hapten complex in the body or reaction may due to drug metabolite.
5. Patient on antihistamines, immunosuppressives, beta blockers, etc.
6. Patient has T-cell-mediated drug hypersensitivity reactions.

TEST PREPARATIONS AND TEST CONCENTRATION

SPT/IDT is generally employed for medications available in the solution form or parenteral preparations. To make different concentration of a drug, 0.9% NaCl is used as diluent. When test drug is available for oral use in tablets/capsule form, it has to be crushed and added with 0.9% NaCl to obtain optimal drug concentration as measured as mg drug/mL vehicle for testing. If the drug to be tested is hydrophobic, a solution is prepared by adding dimethylsulfoxide (DMSO) initially and then diluted with 0.9% NaCl. In such cases, similar concentration of DMSO is used as control.[3]

A major challenge in SPT/IDT is the standardization of test preparation of the drug as this can influence the test result in a significant manner.

Initially, the SPT is done with a low concentration (usually not lower than 1/100 of the solution preparation). If no reaction occurs, 10-fold increases in the test concentration are done until a positive reaction is seen. If no reaction can be elicited by the SPT, intradermal testing starting with a dilution of 1/100 of the SPT concentration is done and the concentration is increased in logarithmic steps (1/10, 1/1) until the final concentration is reached with a positive test reaction after 20 minutes.[2]

SPT/IDT AND COMMON DRUGS IN DERMATOLOGY PRACTICE

As mentioned earlier, although SPT/IDT can be used to detect allergy to various drugs, in day-to-day dermatology practice, it is useful for detecting drug allergy to lidocaine and β-lactam antibiotics.

Intradermal Tests for Lidocaine

Lidocaine as local anesthetic agent is commonly used for infiltration or topical anesthesia in various dermatosurgical procedures. Amide group of agents e.g. lidocaine, mepivacaine, bupivacaine, articaine, and prilocaine are suggested to be less allergenic than ester anesthetics such as benzocaine, procaine, and tetracaine. Type I hypersensitivity reactions are common due to metabolic product, a para-aminobenzoic acid, of ester anesthetic. Although cross-reactivity is common among ester group of anesthetics, it is not common with amide group of local anesthetics (LA).[10] Perhaps, true allergy to LA is rare and reactions are commonly due to preservatives like parabens and metabisulfite used as antioxidants. IDT detects allergic reactions to LA only while toxic or autonomic reactions cannot be tested. A graded concentration of lidocaine is used for testing, beginning with 1:10,000 followed by 1:1000 and 1:100 dilutions.[11]

Intradermal Tests for β-Lactam Antibiotics

Immediate reactions to β-lactam antibiotics are due to β-lactam moiety or side chain. Penicilloyl polylysine (PPL) and minor determinant mixture (MDM) are common penicillin antigens recommended to detect allergy due to β-lactam moiety. As aminopenicillin side chain present in amoxicillin can also cause β-lactam allergy, testing with this side chain or amoxicillin (Ax, 20 mg/mL) determinant is also recommended as PPL

and MDM skin tests will be negative. However, these test kits are now not easily available commercially. It has been suggested that benzylpenicillin (10,000IU/mL) can partially compensate for PPL and MDM's unavailability.[12] When β-lactam antibiotic does not contain benzylpenicillin or amoxicillin, then it can be tested directly.[13] Cephalosporins are β-lactam antibiotics, which have high potential for IgE-mediated urticarial reactions. IDTs have been done in the past by some investigators with variable results. Unlike penicillins, cephalosporins degrade to form heterogeneous reactive antigenic determinants, which are yet to be known.[14] While doing IDT, drugs such as cephalosporins tend to produce nonspecific irritant skin reactions resulting in false-positive reactions. Hence, the optimum concentration of cephalosporins which does not result in irritant reactions should be chosen. However, there is no consensus regarding this. European Network for Drug Allergy/European Academy of Allergy and Clinical Immunology (ENDA/EAACI) Drug Allergy Interest Group recommended a concentration of 2 mg/mL for cephalosporin skin tests.[2] Several other studies recommend a concentration up to 20 mg/mL of cefuroxime, ceftriaxone, cefotaxime, ceftazidime, cefazolin, cephalexin, cefaclor, and cefatrizine, which do not produce irritant reactions and increase the chances of detecting drug hypersensitivity.[15,16] Yoon et al. used concentration of 2mg/mL of all four generations of cephalosporins in a large number of patients (1421) to perform IDT and reported that the IDT for cephalosporin had a sensitivity of 0%, a specificity of 97.5%, a negative predictive value of 99.7%, and a positive predictive value (PPV) of 0%, when challenged with the same drugs that were positive in the skin test. They concluded the routine skin testing with a cephalosporin before its administration is not useful for predicting immediate hypersensitivity because of the extremely low sensitivity and PPV of the skin test.[17]

Although, IDTs are currently used for the diagnosis of immediate hypersensitivity to various drugs successfully, they require further standardization and clinical correlation to impart much needed validity and reliability to these diagnostic techniques.

LEARNING ESSENTIALS

- SPTs/IDTs detect immediate hypersensitivity reactions to drugs.
- IDT to detect hypersensitivity to penicillin and lignocaine should be done by dermatologists in their day-to-day practice to avoid fatal immediate hypersensitivity reaction. This is also important for medicolegal purposes.
- Selection of nonirritant concentration of drugs to be used for intradermal tests is of paramount importance to avoid false-positive reactions. Identification of such nonirritant concentration or standardization of test concentration remains a challenge for a variety of drugs.
- Drug provocation tests can be done with all precautions if the drug is extremely essential for a patient and when SPT/IDT is not possible due to nonavailability of test formulation of a particular drug. In all other cases, if required, it should be done only after SPT/IDT.

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Chapter

10

Patch Testing in Cutaneous Adverse Drug Reactions

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SUMMARY

Cutaneous adverse drug reactions (CADRs) are among the most frequent manifestations of drug sensitivity. They may present with varied morphology ranging from urticaria to Stevens—Johnson syndrome. In this age of polypharmacy, where new drugs are entering into the market every day, it has become essential to document the culprit drugs in a suspected case of CADR. It may be difficult to identify the drug from temporal correlation/history alone.

Drug patch tests are low-risk diagnostic tests based on the principle of delayed hypersensitivity reaction that help in assessing the culpability of the drug without increasing the risk of precipitation of a reaction.

It is easy to perform and any commercially available drug can be used for testing. However, the sensitivity and specificity of patch tests in identifying the offending drug depend on various factors such as type of a CADR, nature of drug, vehicle, duration, and site of patch testing. This chapter deals with the role of patch test in a suspected CADR. It highlights ideal test procedure, technique, precautions, and modifications to be undertaken, with respect to different drugs to avoid false-negative reactions.

It may be worthwhile to remember that patch test although sensitive, may not be positive in all types of drug reactions and in such cases oral provocation test is required to confirm the culprit drug.

INTRODUCTION

Cutaneous adverse drug reaction (CADR) is an undesirable change in the structure or function of skin or mucous membranes induced by either systemic or topical drugs when used in adequate doses and in the correct indications. The frequency of adverse drug reactions (ADRs) has been estimated to be 10%–20% among hospitalized patients and 7% in general population.[1]

In today's age of polypharmacy, patients are often on multiple drugs and it may be difficult to identify the responsible drug solely based on chronology from patient's history. Patch testing with the suspected drugs can be helpful in determining the cause of cutaneous CADR and in studying the pathophysiological mechanisms involved in them.

Drug rechallenge is considered a more definitive test for confirming the culprit drug. However, it is time-consuming when several drugs are suspected and may not always reproduce the skin reaction. Also, it is contraindicated in severe reactions, such as toxic epidermal necrolysis or drug hypersensitivity syndrome.[2] In such situations, complementary clinical and laboratory investigations such as skin tests and radioallergosorbent test (RAST) can help identify the imputable drug. It is important to choose the most appropriate skin test, according to the drug reaction pattern. Drug patch tests (DPTs) are low-risk diagnostic test for CADR as they can reproduce delayed hypersensitivity to drugs without increasing the risk of precipitation of reaction.

TYPES OF DRUG REACTION

ADRs can manifest in several ways and to diagnose and identify the culprit drug, it is important to understand the classification and pathogenesis of ADRS. Rawlins and Thompson[3] classified ADR into four types: (1) type A (augmented) reactions—predictable owing to the pharmacologic or toxic property of the causative drugs and occurring in

80%; (2) type B (bizarre) reaction—not predictable, and occur only in susceptible individuals (10%–15%); (3) type C (chemical) reactions—associated with long-term therapy (e.g. benzodiazepine dependence); and (4) type D (delayed) reactions—carcinogenic and teratogenic effects of drugs.

Type B reactions are mostly immune mediated (allergic) i.e. mediated by specific immune system (IgE or T cell or immune complex mediated) or nonimmune-mediated (nonallergic) i.e. without the involvement of immune system.[4]

Principle of Drug Patch Testing

The basic principle and procedure of patch testing in CADR is same as that of allergic contact dermatitis. Chemical antigens/drugs are mostly recognized by the T cell as haptens bound to self-proteins upon processing by an antigen-presenting cell (APC) and rarely by directly binding to T cell receptor (TCR). On activation, T cells cause antibody production (IgG, IgA, or IgE) by B cells and proliferation of memory T cells to generate clones with specificity for that drug/immunogen. This results in immunological memory and activates immune effector mechanisms resulting in tissue damage. It takes a minimum of 7–10 days to generate immunological memory and to become sensitized. Hence, patient must have had previous exposure to the culprit drug, or there must have been ongoing exposure for at least 7–10 days. The T cell functional profile is critical to the development of subsequent immune response and reaction pattern. Once the particular immune effector mechanism has been generated, the person will react to subsequent exposure to the relevant drug in a similar manner. Patch tests use skin dendritic cells to present chemical antigen to skin-circulating T cells. Th1-specific T cells initiate the inflammation in a positive patch test.

Drug Imputability

Drug imputability can be suspected using the criteria proposed by Moore et al.[5] All the drugs that are taken by the patient during the onset of the CADR, even if they have been prescribed for months, have to be listed including the dates treatment was begun and stopped, interval between the beginning of drug intake and the onset of the CADR, mode of administration, dosage, and the disease that it was prescribed for. Concurrently, the evolution of the CADR must be noted. A previous exposure to the suspected drug or history of a similar CADR in the past can help pinpoint a drug. If any investigations such as oral provocation test, RAST, or a lymphocyte transformation test have been performed, they should be included.

CLINICAL TYPE OF DRUG REACTIONS

Only delayed-type hypersensitivity reactions can elicit a positive patch test. It may be possible to determine the culprit drug in eczematous drug reaction, systemic contact dermatitis, maculopapular drug rash, DRESS, FDE, and less commonly in SJS/TEN using patch test (Table 10.1). However, these are not absolute and are dependent on various other drug factors such as drug type, drug concentration, vehicle, and excipients used, besides the clinical type of reaction.

Table 10.1: Different type of drug reactions and patch test positivity

Drug reaction	Patch test positivity
Maculopapular rash	Useful (positive in 10%–40% of the series)[6,7]
Localized eczema due to heparins	Can be positive[8]
Systemic drug-related intertriginous and flexural exanthema (SDRIFE)	Useful (maybe 52%–82%)[9]
Fixed drug eruption (FDE)	Useful on previously affected site (positive in 40%–87% of the cases)[10,11]
Acute generalized exanthematous pustulosis (AGEP)	Useful (positive in 50%–58% of the cases)[12,13]
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Useful (positive in 32%–64% of the cases)[14]
Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN)	Can be done but are rarely positive in 9%–25% of the cases[15–17]

Methodology

Procedure and Site

Patch tests are usually performed on the unaffected and untreated skin over the upper back using Finn chambers or an equivalent and fixed with hypoallergic tape. However, in certain CADRs, such as FDEs and systemic drug-related intertriginous and flexural exanthema, and less commonly SJS/TEN[18] or maculopapular rash[19] caused by specific drugs, patch tests may only elicit positive responses if applied to previously affected sites. Patients are instructed to leave the patches in place for next 48 hours and to avoid rubbing, scratching, or wetting them. It is advisable to take readings after 20 minutes for immediate hypersensitivity reactions such as urticaria in case of β-lactam antibiotics, neomycin, and gentamycin. In drug-induced photosensitivity, both patch and photopatch tests are to be performed with the suspected

drugs. The irradiation for drug photopatch tests is performed usually on day 1, or less commonly on day 2 with a 5 J/cm^2 ultraviolet A (UVA) irradiation.[20]

Precautions

Systemic glucocorticoids and immunosuppressives should be discontinued at least 1 month before patch testing.[21] Topical glucocorticoids should not be applied at the site of patch tests for at least 2 weeks before the test. Large doses of topical glucocorticoids away from the test site may have the same effect as low doses of systemic glucocorticoids.[22] Strong UV exposure to patch testing site will diminish test reactivity.[20] Antihistamines do not interfere with test results and can be allowed during/before patch testing.

Time

There are slight differences among different guidelines regarding the time interval between the complete healing of cutaneous adverse reactions and patch testing, the time of readings, and reporting, which are summarized in Table 10.2. The criteria of the International Contact Dermatitis Research Group are similar to those of the European Environmental Contact Dermatitis Research Group.[23]

Table 10.2: Guidelines for drug patch testing[20,21]

Characteristics	European Society of Contact Dermatitis (ESCD)	European Network on Drug Allergy (ENDA)
Time interval between complete healing and patch test	6 weeks to 6 months	3 weeks to 3 months
Reading	20 minutes, day 2 ,4 and 7	Day 2, 3, and 4
Scoring	International Contact Dermatitis Research Group (ICDRG) criteria	European Environmental Contact Dermatitis (EECDRG) criteria
Percentage of drug used	30	20

Source: Modified from Romano et al.[22]

Drug Concentration

The threshold of sensitivity for many pure substances has not been determined in DPTs. Ideally, pure drug compound should be tested at a concentration of 1%–10% wt/wt in an appropriate vehicle.[24] Lower concentrations are to be used in extremely severe CADR and increased gradually if patch test results were negative. Acyclovir, carbamazepine, and pseudoephedrine should be tested with low concentration to avoid a severe reaction.[23] Colchicine and celecoxib induce irritant reaction and need to be applied at lower concentrations to avoid a false-positive reaction[21] (Table 10.3).

Table 10.3: Different drugs and their concentration and vehicle required for patch testing

Drug	Vehicle	Concentration (%)	Comments
Acyclovir	Pet/Aq	1–10	Aq vehicle if negative with pet[25]
β-lactams	Pet	5–10[26]	Lower concentration
Carbamazepine	Pet	1–10	Lower concentration
Celecoxib	Pet	1–10	Frequent false positive at high concentration[27]
Chloroquine	Pet	30	No true positive. False positives[28]
Captopril	Pet	1	False positive results[28]
Corticosteroids	Aq/Al	Up to 30	Alcohol vehicle. False positive in upto 80%[29]
Cotrimoxazole	Dimethyl sulfoxide (DMSO)	10, 20, or 50	Negative in pet[16]
Desloratadine	Pet	1[30]	Lower concentration required
Famciclovir	Pet	50[25]	Requires higher concentration
Ganciclovir	Aq	20	Higher concentration
Omeprazole	Pet/Aq	30	No true positive[28]
Radio contrast medium (RCM)		Pure	No dilution required[31]
Steroid hormones	Pet/Aq/Al	Up to 30	Alcohol vehicle if negative with Pet[29]
Teicoplanin	Aq	4[32]	Lower concentration
Vancomycin	Aq	0.005[32]	Very low concentration

Note: Pet: Petrolatum; Aq: Aqueous; Al: Alcohol.

When it is not possible to obtain the pure drug, the prescribed form of the drug (tablet or capsule) can be used. When a commercial form of the drug is used, a 30% by weight concentration of the powdered

drug in white soft paraffin can be used.[20] When the weight of the active drug and excipients is known in the commercialized form, a concentration that leads to a final 10% concentration of the active drug can be used.[33] Preparations for patch tests are made; one patient at a time just before the application as their stability is not known. It is imperative to test preservatives, coloring agents, and excipients in both undiluted and diluted form.

Commercial standardized drug allergen series are now available (e.g. Chemotechnique laboratory, Velinge, Sweden) with the pure active products. However, there are a limited number of drug allergens in the series and almost every drug can induce a CADR. Nevertheless, the list includes drugs more frequently responsible for delayed CADRs such as antibiotics, antiepileptic, and nonsteroidal anti-inflammatory drugs (NSAIDs) (Table 10.4). No controls are needed for these allergens. These series have made patch testing with drugs simple, allowing testing several drugs at the same time and also testing with analogous chemicals to study cross-reactions and find possible replacement drugs.

Table 10.4: The CADR series

Drug name	% petrolatum
Penicillin G potassium salt	10.0% pet
Trihydrate	10.0% pet
Dicloxacillin sodium salt hydrate	10.0% pet
Cefotaxime sodium salt	10.0% pet
Doxycycline monohydrate	10.0% pet
Minocycline hydrochloride	10.0% pet
Erythromycin base	10% pet
Spiramycin base	10.0% pet
Clarithromycin	10.0% pet
Pristinamycin	10.0% pet
Co-trimoxazole	10.0% pet
Norfloxacin	10.0% pet
Ciprofloxacin hydrochloride	10.0% pet
Carbamazepine	1.0% pet
Hydantoin	10.0% pet
Diltiazem hydrochloride	10.0% pet
Captopril	5.0% pet
Acetylsalicylic acid	10.0% pet
Diclofenac sodium salt	1.0% pet
Ketoprofen	1.0% pet
Piroxicam	1.0% pet
Acetaminophen	10.0% pet
Acyclovir	10.0% pet
Hydroxyzine hydrochloride	1.0% pet
Hydrochlorothiazide	10.0% pet
Clindamycin phosphate	10.0% pet
Cefradine	10.0% pet
Cephalexin	10.0% pet
Ibuprofen	10.0% pet
Lamotrigine	10.0% pet
Cefuroxime sodium	10.0% pet
Cefixime	10.0% pet
Imipenem monohydrate	10.0% pet
Cefpodoxime proxetil	10.0% pet
Potassium clavulanate	10.0% pet

Drugs

Drugs with highest frequencies of positive patch tests are anticonvulsants (carbamazepine and phenytoin), β-lactam antibiotics, co-trimoxazole, corticosteroids, diltiazem, diazepam, tetrazepam, and pristinamycin.[24,33] Piroxicam, ketoprofen, fluoroquinolones, and flutamide often elicit positive photopatch tests.[34]

Certain drugs, such as allopurinol[35], can produce negative patch test result despite being the suspected drug. This could be attributed to the interaction between skin barrier function with drug molecular factors such as molecular weight and lipophilicity playing a role. It could also be due to impaired metabolic capacity of skin to generate haptens or T-cell-dependent response.

Vehicle

The best vehicle to prepare DPT is yet to be determined. Petrolatum is the most accepted and commonly used vehicle for patch tests worldwide. Certain drugs like steroid hormones have to be tested after diluting with alcohol, and acyclovir and ganciclovir with water to avoid false-negative results.[36] (Table 10.3). Ideally, testing should be done using all the vehicles and in different concentration especially if test results are negative.

Reporting

The results of patch testing are reported according to the ICDRG criteria for patch test reading as negative, doubtful, or positive results on days 2 and 4 (Table 10.2). In negative cases, additional readings on day 7 are recommended especially in β-lactams[37] and glucocorticoids.[36] Patch test reactivity can rarely occur in less than 2 days (after 24 hours), as in the case of abacavir.[38] Sometimes, patch test site may have a pustular or bullous reaction that mimics the histopathology and clinical pattern of the CADR.

Factors Affecting Patch Test Result

Epidermal permeability barrier is effective in blocking the penetration of water-soluble molecules, but lipid-soluble substances can penetrate easily. This can easily be disrupted by tape stripping, 10–15 times, which facilitates the penetration of water-soluble and large drug molecules.[39] Certain drugs such as bleomycin or teicoplanin due to their large size require disruption of the stratum corneum barrier

to penetrate sufficiently.[40,41] Controls are important for high predictive value of positive results and to exclude irritant reactions. The test substances and vehicles need to be tested in healthy control subjects before actual testing in CADR patients.

USEFULNESS OF DRUG SKIN TESTS TO STUDY CROSS-REACTIVITY BETWEEN DIFFERENT DRUGS

Patch tests can also help to study the cross-reactivity between drugs in CADRs, e.g., cross-reactions are common between aromatic anticonvulsants, lamotrigine, and valproic acid[42], among β-lactam antibiotics[24,43] and acyclovir, valaciclovir, and famciclovir[44], etc. because they share common chemical structure. This can help generate a safe drug list for the patient. Patch and photopatch tests may not give similar results or cross-reactivity in drug-induced photosensitization due to different photosensitization potential of chemically similar compounds.[34]

Safety

DPTs can rarely reinduce the delayed CADR as reported with acyclovir, pseudoephedrine, pristinamycin, and carbamazepine[45]; however, the risk is very low. For safety reasons, the patient should be observed for approximately half an hour after application of the test material. The risk of serious CADR with patch testing is considerably lower than that of intradermal tests or oral provocation test.

Relevance and Specificity of Drug Patch Tests

False-negative reactions can occur due to technical problems (low concentration or wrong vehicle, deficient skin penetration, and wrong timing of performing patch test), nonimmune reaction, responsible hapten (drug metabolite) is not formed in the skin, and concomitant factors such as a viral infection or other drugs, not being present at the time of testing.[28]

False-positive results may be because of excipient, preservative, or stabilizer in the commercialized drug.[28] It may also be due to the irritant reaction if higher concentration is used or cross-reaction between drugs. In recently published study, sensitivity, specificity, and positive and negative predictive values of drug patch test in CADRs were found to be 32%, 92%, 80%, and 57.5%, respectively. Thus, if negative, it does not exclude the possibility of a drug in causing CADR; instead they reduce the need for oral provocation testing, if positive.

It is beneficial as the procedure for conducting oral provocation tests in delayed reactions are not standardized and it is not clear which dose should be used and for how many days re-exposure should be done.

CONCLUSION

Drug patch testing is a safe procedure that can be used to determine the culprit drug in several types of CADRs. It is easy to perform and any commercial drug can be used for testing if the pure drug is unavailable. It is worthwhile to completely familiarize oneself with the procedure before performing the test so that specific site and drug concentration can be used to avoid false-negative/positive results.

A patch test is an ideal early investigation in CADR patients considering its low risk as compared to intradermal or oral provocation tests. Once a patient has suffered a CADR, clear information must be provided to him/her regarding the type of CADR, names of the culprit drugs, potentially cross-reacting drugs, and drugs that can be safely given in case of a similar episode after testing. All these details encompass the complete evaluation of a CADR. Patients should be advised to carry a card with them that lists drug allergies and/or intolerances, especially if they have had a severe reaction like SJS/TEN or DRESS. Certain drug reactions may have genetic predisposition (like in SJS/TEN) and family counseling is part of the care plan.

However, there is a major conundrum in the field of diagnostic patch testing in drug reactions. It is necessary to standardize the patch test procedure in CADRs to compare results in larger multicenter studies and determine concentration thresholds of drugs to avoid false-positive/negative results.

LEARNING ESSENTIALS

- It is worthwhile to perform patch tests on patients with a suspected drug eruption.
- They can help in identifying the culprit drug in CADR. Also, it can provide information about drug cross-reactions and help in avoiding further reintroduction of the drug in the patient, which can lead to severe consequences.
- Patch tests are frequently positive in maculopapular exanthema, AGEP, systemic contact dermatitis, DRESS, and FDEs and rare in SJS/TEN, drug-induced vasculitis, etc.
- Patch tests are best performed 3–6 weeks after the CADR has subsided.
- Concentration of drug used, vehicle, and time of reporting may vary with different drugs and it is ideal to know them before performing the test.
- It is a very safe procedure with a low risk of precipitation of a drug reaction in contrast to oral provocation tests.

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Chapter

11

Drug Provocation in Cutaneous Adverse Drug Reactions

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SUMMARY

Cutaneous adverse drug reactions (CADRs) are frequently encountered by dermatologists. Although single drug responsible for CADR may be easily deciphered, clinical presentation and history taking may not be sufficient to find out the cause of drug reaction in cases where multiple drugs are implicated. Though the importance of a detailed history taking cannot be overemphasized and considering the multitude of drug preparations available in the market coupled with the inadequacy of currently available *in vitro* tests for diagnosing CADRs, performing a drug provocation test is the only reliable way to confirm the diagnosis. Drug provocation is considered to be the gold standard to confirm or refute the diagnosis of a CADR. However, there is no standardization for testing of various categories of drugs implicated in different CADR protocols and is largely based on a physician's experience as well as the individual case. This chapter aims to summarize the current evidence on drug provocation in the literature and to provide information regarding the approach for drug provocation testing.

BACKGROUND

Drug provocation is the controlled administration of a drug, under supervision, in order to establish a diagnosis of a cutaneous adverse drug reaction (CADR) or in some cases also to provide a list of alternative drugs that can be safely taken by the patient. Establishing the culprit drug in a CADR may be straightforward in cases where a single drug has been administered in the period before onset of the reaction. Diagnosis, on the other hand, may be difficult when more than one agent is incriminated. Theoretically, the list of investigations for a CADR include *in vitro* tests, *viz.*, transformation assay, lymphocyte toxicity assay, cytokine assays, flow cytometry analysis, as well as *in vivo* tests, such as patch testing, oral drug challenge, and drug provocation.[1–6] As the clinical relevance of *in vitro* as well as other *in vivo* tests can be determined by drug provocation testing, it is considered to be the gold standard for establishing the diagnosis of a CADR. In addition, since such *in vitro* and *in vivo* tests depend on the presumed mechanism of action in a particular CADR, which may not be the actual biological phenomenon, the fallacies and limitations of such tests are obvious.

WHEN TO PERFORM A DRUG PROVOCATION?

A dermatologist may encounter CADRs manifesting in various forms. Although the reaction may be trivial at times, establishing the causative agent is of utmost importance, not only to prevent a recurrence in the future but also to reduce the morbidity of patients who may develop a lifetime phobia of drug reactions. History alone is usually not adequate for diagnosing a CADR. Prior studies have shown that less than 20% of patients were found to react to the drug on provocation when the diagnosis was based on history alone.[7] Furthermore, the poor record of medication received by the patient, self-medication by the patient with over-the-counter (OTC) products, and also non-OTC products sold by chemists without prescription of some of the active ingredients and excipients not declared by the manufacturer add to the inaccuracy of the history of drug intake.

Drug provocation is needed in cases where the diagnosis of drug reaction is doubtful. For instance, patients with spontaneous urticaria and angioedema may complain of exacerbation by nonsteroidal anti-inflammatory drugs (NSAIDs). In such cases, controlled administration of NSAID in

supervised setting may help to confirm the drug-induced exacerbation. The clinical presentation may sometimes be very suggestive of cutaneous drug reaction e.g. in fixed drug eruption. However, problems may arise when multiple drugs have been taken prior to the onset. It may be worthwhile to do a positive drug provocation testing in such cases to confirm the causative agent. Though there is no consensus regarding provocation testing in cases of life-threatening CADRs, such as toxic epidermal necrolysis (TEN), there are case series in which patients with TEN have been safely administered the implicated agents orally in increasing doses to confirm the offending drug.[8] Such proactive steps of drug provocation are prudent as any inadvertent or uninformed intake of the culprit drug in future has more risk of life-threatening CADR as compared to a minimal discomfort or effectively mild CADR in a supervised setting of drug provocation. With drugs that have limited usefulness to the patient in the future, provocation testing may not be required if the patient is properly educated regarding avoidance of even the widely used drugs for common ailments without recording it.

The indications for oral provocation in CADR are as follows:

1. To confirm the culprit drug
2. To confirm cross-reactivity, with structurally related drugs
3. To provide alternative most likely tolerated drugs
4. To exclude drug reactions in patients with drug phobia

WHEN NOT TO PERFORM PROVOCATION TESTING?

Drug provocation should be done with caution under medical supervision. One may defer doing a provocation testing in case of pregnancy, severe anaphylactic CADR, uncontrolled asthma or underlying severe cardiac, and renal or hepatic disease. However, there are certain exceptions to these situations, when the suspected drug is essential e.g. in case of penicillin hypersensitivity in pregnancy.

The literature has controversial data regarding the provocation testing in patients with toxic epidermal necrolysis and bullous fixed drug eruption. However, in authors' experience, these patients have been safely provoked under strict medical supervision, with no untoward incidents occurring as a result of drug provocation till date. It goes without saying that the treating dermatologist has the onus to control the CADR when provocation is performed. In such a situation, the dose of systemic corticosteroids or any appropriate medication should be preplanned, and it should be on the higher side as the requirement of such doses is only for a very limited period. Half-hearted drug provocation or poor planning of the control should be avoided. In a series of cases of toxic epidermal necrolysis, four cases were treated with corticosteroids. Provocation was undertaken after complete healing during the hospital stay. Provocation was performed with antitubercular drugs, phenytoin, co-trimoxazole, trihexyphenidyl, chlorpromazine, trifluperidol, lithium, and carbamazepine, without any untoward reactions.[8]

PRACTICAL ASPECTS: DRUG PROVOCATION TESTING

Ethical Issues

Like for any other medication, procedure, or surgery, the treating person always has to weigh the risk involved against the benefits achieved. The drug provocation in a near-comprehensively controlled setting with deliberate introduction of each drug, prior knowledge of the expected adverse reaction, and ability to intervene and control said reaction promptly has minimal risk. Further, in future, it will prevent delayed medical intervention to such a reaction, and also protect the patient from inadvertent intake of the offending drug, in a scenario where the patient may be unattended. These facts should be informed and explained to the patient and a written consent should be signed by the patient before drug provocation.

Routes of Administration

Drug provocation testing can be done by different routes that include oral, parenteral, cutaneous, bronchial, and conjunctival. Ideally, the route of administration for drug provocation should be the same as that during the drug reaction. Of all the routes, oral route is preferred due to the ease of controlling a reaction developing by oral provocation as the drug absorption through oral route is slower.

Agents for Provocations

All the incriminated agents should be carefully enlisted. It is of utmost importance to test the individual components of the drug instead of the whole preparation. As far as possible, the active ingredients should be tested separately from the additives as these may also led to the reaction. For instance, additive carboxymethyl cellulose present in injectable glucocorticoid preparations has been found to cause hypersensitivity reactions.[9] Though rare, it is possible that in a combination drug one agent is acting as the main offender and some innocuous molecules are acting as a hapten.

Therefore, if all the single agents are found to be safe, the suspected combination can also be used at the end for provocation.

It is strongly recommended that the drug provocation should be started with a placebo. This will exclude false-positive reactions, and is especially useful in patients in whom anxiety and subjective symptoms are the main features rather than a true reaction. Administering placebo in such cases is reassuring to the patient as well as the treating physician.

Setting and Prior Requisites

A drug provocation testing is carried out under medical supervision with emergency resuscitation equipment on hand and a round-the-clock availability of physician. In a study by Lammintausta and Kortekangas-Savolainen, patients were allowed to go home 3–4 hours after drug provocation and asked to return in the case of positive reaction.[10] The patient should not be on glucocorticoids or antihistamines as these may mask the early signs of positive reaction. The CADR may have subsided completely before provocation is started. Laboratory abnormalities, if any, should also have become normal. Ideally, the patient should not be on any other medication during provocation testing. However, drugs that have been taken safely for medical reasons requiring treatment may be continued. Resuscitation measures, in case of an emergency, should be available. In case of urticaria, aggravation of spontaneous urticaria coinciding with the drug provocation may lead to a false-positive reaction. Hence, it should be ensured that the disease activity is well controlled before initiation of provocation.

Blinding the patient to the nature of medication used for provocation is important to avoid subjective symptoms, particularly itching and sometimes erythema, which may cause confusion while recording the reactions. In a study, healthy students were administered only placebo capsules and observed over a 3-day period, 41% of individuals complained of subjective symptoms in form of nasal congestion, erythema on skin, and urticaria.[11]

Dose and Order of Drugs for Provocation

Usually the provocation begins with a placebo, which is followed by a graded challenge with the suspected drugs in order of increasing susceptibility i.e. a drug that is least likely to cause a reaction should be administered first, whereas the drug that is most implicated in causation of the reaction should come at the end. This order ensures that if a positive reaction occurs during provocation, the likelihood of interruption in the flow of provocation is low.

The dosage of the drug depends on the clinical suspicion of the drug being implicated as well as the severity of prior reactions. In cases where the drug is not the likely implicated agent, a full dose of the drug may be administered per day. However, if the clinical suspicion is high, a graded challenge, starting with one-fourth or half of the recommended dosage and then daily hiking up the dose to double strength, is performed. Lammintausta and Kortekangas-Savolainen also performed the hiking of the drug on the same day at 3- to 4-hour intervals in cases where lower doses did not lead to any reaction.[10]

In cases where provocation is being performed to administer a safe drug list for likely future use in common ailments, a full dose of each drug is given daily, as the safe drug list is prepared from drugs that are structurally unrelated to the offending agent and are likely to be safely tolerated by the patient. Prior studies have also shown that in case a patient is tolerating the safe drug provocation well, the provocation may be accelerated to one drug every 12 hours to shorten the hospital stay of the patient.[12] However, for practical reasons, one drug in a day (24 hours) is the best method and ideally it should be performed during forenoon, so that even a mild change can be easily seen in daylight and the availability of physician is convenient.

Recording of Reactions

Documentation of each drug with the timing of administration as well as the symptoms or signs developed, if any, is of utmost importance. In addition, objective evidence in the form of photographic documentation of positive reactions and biopsy (in case of doubt regarding diagnosis) may be useful. If no symptoms appear from a particular dose of a drug, then the same drug is administered in a graded manner until the therapeutic dose is reached, followed by the next drug. Comprehensive and accurate recording of the positive reactions is necessary. In case of a doubtful reaction, repeated provocation with a higher dose should be performed the next day. In case of a positive reaction, adequate treatment with appropriate agents, *viz.,* antihistamines and oral corticosteroids, depending on the type and severity of reaction, should be administered. After a positive reaction, relevant investigations should also be performed. For example, evaluation for eosinophilia and deranged liver enzymes should be carried out in case of development of a drug reaction with eosinophilia and systemic symptoms (DRESS). The treatment given for the positive reaction along with the response should also be documented. Complete subsidence of the positive reaction is followed by the provocation with next agent. The drugs found to show positive reactions in oral provocation in various series are shown in Table 11.1.

Table 11.1: Results of oral provocation in different studies

Author(s), year	Diagnosis	Number of patients with positive reaction/number of patients tested	Drugs implicated in positive reactions
Pasricha[13], 1979	Fixed drug eruption (FDE)	28/40	Tetracyclines(6), analgin (metamizole) (6), oxyphenbutazone (5), phenobarbitone (4), sulfadiazine (3), sulfaphenazole (2), penicillin (1), sulfadimethoxone (1), Saridon (1), sulfadimidine (1), and sulfamethoxypyridazine (1)
Quiralte et al.[14], 1996	NSAID intolerance	80/240	Diclofenac (19), piroxicam (17), dipyrone (16), acetyl-salicylic acid (15), ketoprofen (10), mefenamic acid (9), paracetamol (6), diflunisal (4), isonixin (3), clonixin (1)
Pasricha et al.[8], 1996	Toxic epidermal necrolysis	4/4	Thiacetazone (1), co-trimoxazole (1), phenytoin (1), carbamazepine (1)
Gupta[15], 2003	FDE	37/40	Co-trimoxazole (21), oxyphenbutazone (9), metamizole (3), tetracycline (3), piroxicam (1)
Lammintausta and Kortekangas-Savolainen[10], 2005	Exanthema, angioedema, urticarial, FDE	136/784	Sulphonamides (26), trimethoprim (18), amoxicillin (11), nitrofurantoin (8), penicillin (8), tetracycline (6), acetyl-salicylic (7), paracetamol (3), ibuprofen (2), carbamazepine (6), phenytoin (6), captopril (3), diltiazem (3)
Ramam et al.[12], 2012	Safe drug list generation in various drug reactions(urticarial reactions), angioedema, FDE, maculopapular drug rash, self-reported multiple drug reactors, Stevens–Johnson syndrome, and toxic epidermal necrolysis	34 (true reactions), 27 (spurious reactions)/100	Isoniazid (2), ethambutol (5), rifampicin (1), pyrazinamide (1), streptomycin (1), phenytoin (2), ibuprofen (5), nimesulide (5), diclofenac sodium (3), dapsone (1), metronidazole (1), ornidazole (1), ciprofloxacin (4), norfloxacin (1), tinidazole (1), sulfadoxine–pyrimethamine (1), tetracycline (1), griseofulvin (1), cefadroxil (1), amoxicillin (1), sulfasalazine (1), aspirin (1)

A list of drugs used for provocation testing with clear mention of the generic names should be provided to the patient at the end of testing. Written instructions regarding the avoidance of agents to which the patient has reacted positively should be given. Counselling about avoidance of these agents is extremely important and if possible, immediate family members should also be involved in this. A clear and comprehensive write-up on the medical record about the positive drug provocation is a must and the dermatologist should not limit himself to just meek advice such as “avoid xyz drug in the future”.

LIMITATIONS OF DRUG PROVOCATION

The variation in the type of cutaneous adverse reactions as well as the multitude of preparation of drugs available in the market makes it difficult to standardize drug provocation testing. Hence, the testing is largely individual based with lack of uniform protocols for specific reactions.

LEARNING ESSENTIALS

- Oral provocation is an important tool to confirm as well as refute a CADR. In view of limited availability and reliability of other investigations available for CADRs, oral provocation is strongly recommended as the first-line investigation for a patient with CADR.
- Graded challenge, starting with a placebo, moving on to the other drugs in ascending order of susceptibility, is recommended. The provocation should be performed under medical supervision. In the end, explicit instructions regarding the agents found to be safe and those drugs to which patient has reacted should be provided.
- The rationale and advantage behind being proactively in favor of drug provocation is that it is attempted in a controlled setting with deliberate introduction of each drug, prior knowledge of the expected adverse reaction, and to intervene and control the reaction promptly should it occur. Further, it may help to prevent delayed medical intervention to such a reaction, and also protect the patient from inadvertent intake of the offending drug, in a scenario where the patient may be unattended.

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Chapter

12

Histopathology Aid in Cutaneous Adverse Drug Reactions

Sujay Khandpur • Sanjay Singh

SUMMARY

- Cutaneous drug reactions are an important cause of morbidity and in some conditions even mortality.
- Drug reactions have various mimickers from which it needs to be differentiated so that prompt treatment can be initiated.
- Besides drug provocation test, there are no reliable methods for diagnosis of a drug reaction.
- Histopathological evaluation is an important diagnostic tool in the diagnosis of certain drug reactions.

INTRODUCTION

Cutaneous adverse drug reactions are unintended and undesired cutaneous effects of medications/agents that are used for prevention and management of disease. In view of the continuously increasing number of medications, such reactions have become extremely common. Any drug can cause a skin eruption, although certain classes of drugs are incriminated more often than others. Major offenders include antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), psychotropic agents, β-blockers, calcium channel blockers, thiazides, angiotensin-converting enzyme (ACE) inhibitors, etc. Adverse drug reactions account for between 0.36% and 6% of hospital admissions.[1,2] Most reactions are of milder severity, although some are very severe and can lead to significant morbidity and sometimes mortality.

Certain drug reactions present with several inflammatory histological patterns that overlap with other dermatological disorders (i.e. psoriasiform, spongiotic, and interface vacuolar.), whereas others are quite characteristic for a particular drug, and a skin biopsy undertaken at an appropriate time can, to a large extent, sort out the diagnosis and differentiate it from its close mimickers.

A variety of cutaneous manifestations can occur following drug exposure and are as follows:

MORBILLIFORM DRUG ERUPTION/ MACULOPAPULAR EXANTHEM

Maculopapular exanthem (MPE) consists of macules and papules that do not form a scale. It is the commonest drug-induced adverse skin reaction.[1] Usually it develops within a few days to weeks after initiation of a new drug and resolves in 2 weeks after cessation of the causative medication. Common drugs implicated include anticonvulsants, NSAIDs, antitubercular drugs, antiretroviral drugs, allopurinol, and antibiotics.

Histological Features

The histological features of a drug exanthem are often subtle. The epidermis is usually unremarkable. Focal parakeratosis is commonly seen in stratum corneum. Lymphocytic exocytosis, basal cell liquefactive degeneration, spongiosis, and presence of a few dyskeratotic keratinocytes are considered to be the characteristic changes. The dermis shows mild-to-moderate lymphocytic and histiocytic infiltrate in perivascular location with variable numbers of eosinophils and neutrophils. There may be marked dermal edema and red cell extravasation (Fig. 12.1).

Naim et al.[3] evaluated 60 biopsy specimens from 48 MPE patients. The most consistent features were spongiosis (97% of biopsies), mild epidermal hyperplasia (72%), lymphocytic (82%) and neutrophilic

(32%) exocytosis, focal basal cell degeneration (97%), and occasional necrotic keratinocytes (32%). There were dermal perivascular inflammatory infiltrate in all of the cases, which was superficial in 72% of biopsies and superficial and deep in 28% of biopsies along with papillary dermal edema in 85% biopsies. Exanthems induced by anticonvulsants and anxiolytics predominantly had neutrophils and large lymphocytes.

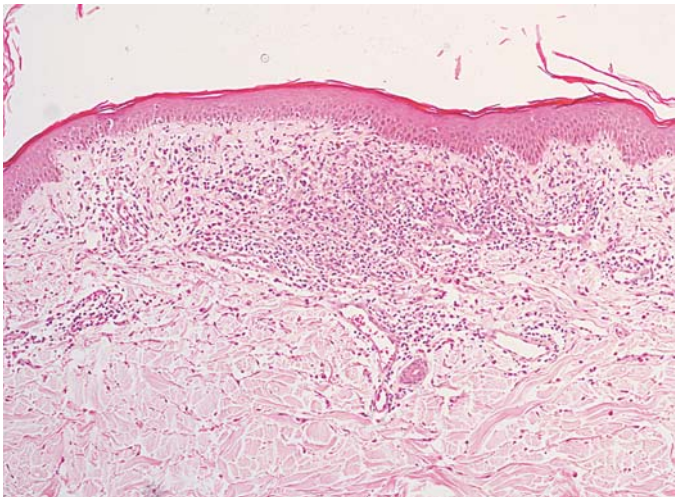

Fig. 12.1: A case of drug-induced MPE showing moderately dense infiltrate of lymphocytes admixed with eosinophils in papillary dermis. Many dilated capillaries with RBC extravasation are also seen (H & E, ×4).

Wang et al.[4] have tried to differentiate drug-induced exanthem from viral exanthem on basis of FAS-ligand staining and eosinophils in biopsy specimens. Of the 10 cases of drug-induced maculopapular rashes, 5 cases (50%) showed positive staining with FAS-L, whereas 1 (10%) case of nondrug-induced rash showed positive FAS-L staining. Moderate-to-dense eosinophilia was seen in 6 of 10 specimens of drug rash, whereas only 2 of 10 cases of nondrug maculopapular rash showed this feature. About 70% of drug-induced and 40% of other exanthems displayed basal vacuolar degeneration.

DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRUG-INDUCED HYPERSENSITIVITY SYNDROME)

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a distinct, idiosyncratic, severe drug reaction, developing 2–8 weeks after drug initiation and characterized by fever, rash, lymphadenopathy, peripheral eosinophilia, and mild-to-severe systemic presentations including hepatic involvement (raised transaminases), myocarditis, interstitial pneumonitis and nephritis, thyroiditis, meningitis, and encephalitis.[5,6] Important implicated drugs are aromatic anticonvulsants (phenobarbital, carbamazepine, and phenytoin), lamotrigine, sulfonamides, minocycline, and allopurinol.

Histological Features

These include dermal edema, perivascular eosinophilic and lymphocytic papillary dermal infiltrate along with extravasated erythrocytes. The infiltrate is generally denser than other drug reactions. Atypical lymphocytes may also be present and can form a lichenoid infiltrate with epidermotropism, resembling mycosis fungoides. Granulomas may occasionally be observed in the superficial dermis.[5]

Ortonne et al.[7] in their retrospective study on 50 skin biopsies from 36 DRESS patients observed diffuse parakeratosis (84%) and foci of lichenoid interface dermatitis (76%), particularly involving the adnexa, apoptotic keratinocytes in 60% cases, neutrophilic exocytosis in 12%, and subcorneal pustules in 18%. Mixed cell infiltrate was present in the dermis. Plasma cells were present in 18%, whereas neutrophils in 42% cases. Only 20% of skin biopsies showed significant eosinophilic infiltrate. One-third of cases showed atypical lymphocytes resembling Sezary cells. Nuclear dust was commonly seen, but features suggestive of vasculitis were not observed. Superficial infiltrate was located in 88% biopsies, especially around capillaries (73%). The density of inflammatory infiltrate was mild (42%) or moderate (50%). Overall, various inflammatory reaction patterns were observed with commonest being interface dermatitis (74%) and eczematous (40%), followed by erythema multiforme (EM)like (24%) and acute generalized exanthematous pustulosis (AGEP) like (20%).

Skowron et al.[8] evaluated histopathological features of 13 cases of MPE, 13 of severe MPE (sMPE), and 45 of DRESS syndrome. Spongiosis was almost similar in all three groups (69%, 61%, and 55%, respectively), whereas spongiform pustules slightly increased from MPE to sMPE and DRESS syndrome (7%, 15%, and 26%, respectively). Keratinocyte damage was rare in MPE, present in sMPE, and frequent and significant in DRESS syndrome (7%, 23%, and 53%, respectively). In the dermis, the density of inflammatory infiltrate increased from MPE to sMPE and DRESS syndrome (38%, 46%, and 75%, respectively). Dermal eosinophils and neutrophils were observed in 69% and 38.5% cases, respectively, in MPE and sMPE but in greater number of DRESS cases (84% and 53.3%, respectively). Atypical lymphocytes were observed in 0%, 23%, and 35% cases of MPE, sMPE, and DRESS, respectively. Leukocytoclastic vasculitis and a deep dermal infiltrate were observed exclusively in DRESS syndrome.

Another study[9] that compared histopathological features of DRESS syndrome (32 patients) with MPE (17 patients) showed major histopathological changes in DRESS syndrome to be dyskeratosis (97%), spongiosis (78%), basal cell vacuolization (91%), and a perivascular lymphocytic (97%) and eosinophilic infiltration (72%), with severe dyskeratosis, epidermal spongiosis, and severe interface vacuolization being significantly more prominent in DRESS.

URTICARIAL REACTIONS, ANGIOEDEMA, AND ANAPHYLAXIS

Clinical Features

Drug-induced urticarial reactions are the second commonest cutaneous drug reactions.[10] They are characterized by pruritic, erythematous, and edematous wheals. Involvement of the deeper dermis and subcutaneous fat causes angioedema. Urticarial reactions may occur secondary to intake of aspirin, penicillin, ACE inhibitors, and blood products or agents, which directly stimulate mast cells i.e. opiates, curare, vancomycin, polymyxin B, and radiocontrast media.

Histological Features

This includes dermal edema with mild perivascular and interstitial mononuclear cell infiltrate admixed with eosinophils (Fig. 12.2). The complement-mediated form of urticaria demonstrates neutrophilic infiltrate with dermal edema. Urticarial vasculitis can be differentiated from urticaria by the presence of fibrinoid necrosis of vessel wall, perivascular infiltrate of neutrophils, karyorrhexis, and red blood cell (RBC) extravasation.[11]

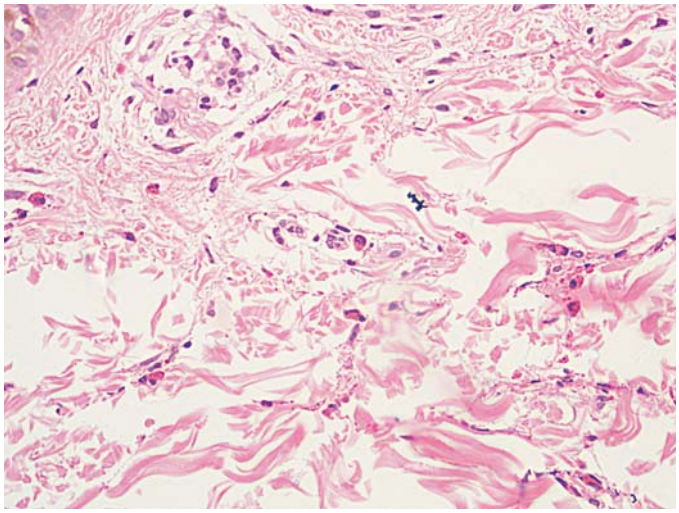

Fig. 12.2: A case of drug-induced urticaria showing perivascular and interstitial infiltrate of eosinophils admixed with few lymphocytes, mild papillary dermal edema present (H & E, ×10).

SERUM SICKNESS/SERUM SICKNESS-LIKE DRUG REACTIONS

Serum sickness represents a type 3 immune complex–mediated reaction. It presents with an erythematous maculopapular or urticarial lesion or with palpable purpura, accompanied by fever, arthralgia, myalgia, and various systemic symptoms i.e. arthritis, glomerulonephritis, myocarditis, and neuritis. The cutaneous lesions are seen on the sides of the fingers, toes, and hands at first, which then becomes more generalized. Usually, there is 1–3 weeks of latency period of development of symptoms after administration of serum or vaccine. Other drugs implicated include phenytoin, phenylbutazone, and carbamazepine, antibiotics particularly cefaclor, cefprozil, ciprofloxacin, minocycline, amoxicillin, and cotrimoxazole and therapy with monoclonal antibodies such as rituximab, infliximab, and omalizumab.[12,13]

Histological Features

Histopathological features include mild perivascular mononuclear cell infiltrate with neutrophils and eosinophils and dermal edema.[12,13]

PHOTOTOXIC AND PHOTOALLERGIC REACTIONS

About 8% of cutaneous drug reactions manifest as photosensitivity.[14] They are of two types: Phototoxic and photoallergic, of which phototoxic reactions are more common. Acute phototoxicity manifests as exaggerated sunburn reaction with erythema, edema, and vesiculation. Pigmentary alteration may also be a manifestation of phototoxicity.

The clinical appearance of photoallergic drug reaction includes eczematous and lichenoid dermatitis. The rash commonly develops 24 hours or more after sun exposure. Unlike phototoxic reactions, photoprotected areas may also be affected.

Histological Features

Acute phototoxic reaction shows multiple sunburn cells (apoptotic keratinocytes) in the epidermis, which in severe cases may affect the entire epidermis. Neutrophil/eosinophil exocytosis can also be seen in variable amount. Spongiosis can vary from mild to very severe with formation of spongiotic vesicles. There is a mild dermal perivascular lymphohistiocytic infiltrate with few neutrophils and eosinophils along with mild-to-moderate dermal edema.

Drug-induced photoallergic reaction on histopathology reveals features of acute, subacute, or chronic spongiotic dermatitis, depending on the age of

the biopsied lesions. Chronic lichenified lesions are characterized by compact hyperkeratosis, hypergranulosis, irregular acanthosis, increased epidermal melanization, melanocyte hyperplasia, and pigment incontinence. Papillary dermal fibrosis, telangiectatic vessels, and sometimes fibroblastic giant cells are present. The inflammatory infiltrate is present in perivascular and interstitial location in the papillary dermis, but a chronic actinic dermatitis–like morphology shows a deeper infiltrate as well.

LICHENOID AND INTERFACE DRUG REACTIONS

Lichenoid drug eruption (LDE) is characterized by a symmetric eruption of erythematous to violaceous papules resembling lichen planus (LP), on the trunk and extremities. The lesions may have an eczematous or psoriasiform morphology. Wickham's striae and mucosal involvement are conspicuously absent. The latency period after drug administration and the development of lichenoid lesions is usually long, varying from weeks, months to years. ACE inhibitors, thiazide diuretics, antimalarials, and β-blockers are the commonly implicated drugs.

Histological Features

Histopathologic findings that are common to both LDE and LP include damage to basal epidermal keratinocytes with multiple apoptotic cells (colloid or civatte bodies), a band-like/lichenoid infiltrate at dermoepidermal junction, and pigment incontinence with presence of dermal melanophages.

The findings that favor LDE include focal parakeratosis, apoptotic/dyskeratotic keratinocytes in the upper layers of epidermis, presence of eosinophils within the lichenoid dermal infiltrate, exocytosis of lymphocytes into the upper epidermis, and sometimes a deep perivascular infiltrate.[15,16]

Photodistributed lichenoid drug reactions resemble idiopathic LP more closely than the nonphotodistributed variants.[17]

Lage et al.[16] assessed the histopathological features of LP (16 cases) and lichenoid drug-induced eruption (LDE, 6 cases). Necrotic keratinocytes, plasma cells and eosinophils (66.7% vs 12.5%) in the infiltrate were more common in LDE than idiopathic LP, whereas colloid bodies (93.8% vs 16.7%) were significantly more in idiopathic LP.

FIXED DRUG ERUPTION

Fixed drug eruption (FDE) is a distinctive type of immune-mediated cutaneous drug reaction, characterized by acute onset of reddish-brown to violaceous lesion that has an annular or discoid morphology and recurs at previously affected sites, following drug exposure. They resolve with residual slate-gray hyperpigmentation. The commonly affected sites are the mucosal surface of lip, glans penis, palms, and soles.

Histological Features

It is characterized by an interface lichenoid tissue reaction. There is basal cell degeneration with a lichenoid infiltrate at the dermoepidermal junction and individual keratinocyte necrosis at upper levels of epidermis. Marked pigment incontinence is characteristic. The inflammatory infiltrate is of mixed type consisting of lymphocytes, histiocytes, neutrophils, and eosinophils, and is not only superficial and lichenoid but also situated in the deep dermis, both in perivascular and interstitial locations (Figs. 12.3A and B). Bullous FDE occurs due to marked basal cell damage that leads to formation of cleft at dermoepidermal junction. Late lesions can show only pigment incontinence as the sole histological finding often mimicking LP pigmentosus or ashy dermatoses.

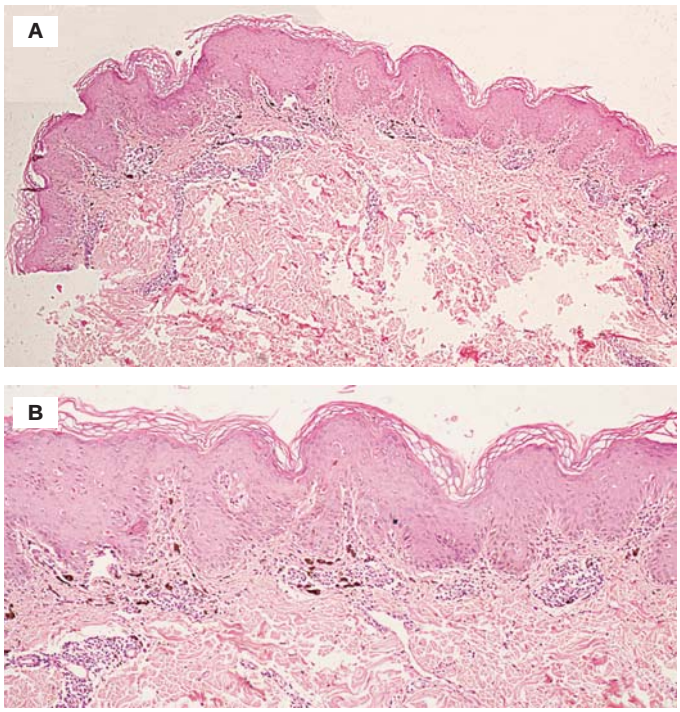

Fig. 12.3: (A) A case of FDE showing irregular acanthosis, upper dermal perivascular lymphocytic infiltrate, and significant pigment incontinence in papillary dermis (H & E, ×4).; (B) A case of FDE showing irregular acanthosis, many discrete necrotic keratinocytes in various layers of epidermis. Upper dermal perivascular infiltrate composed of lymphocytes with occasional eosinophils and significant pigment incontinence (H & E, ×10).

ERYTHEMA MULTIFORME

EM is a hypersensitivity reaction to infections or drugs, manifesting as polymorphous eruption of dusky red to purpuric macules, papules, urticarial plaques, and characteristic "target" lesions, symmetrically distributed, predominantly over the distal extremities. Commonly implicated drugs include anticonvulsants, NSAIDs, antibiotics, phenothiazines, and sulfonamides.[18]

Histological Features

The histopathologic hallmark is a lichenoid tissue reaction and basal cell degeneration associated with scattered necrotic keratinocytes and lymphocyte exocytosis with characteristic "satellite necrosis" of the keratinocytes. A dense superficial dermal lymphohistiocytic infiltrate in lichenoid pattern and also around papillary dermal blood vessels is present[18–20] (Fig. 12.4). Parakeratosis is often absent. EM and FDE share some features. However, absence of acute inflammation in the dermal infiltrate and its occurrence only in the papillary dermis, although not specific, favor EM. Bullous EM, similar to bullous FDE, shows exaggerated basal cell damage leading to formation of a cleft at the dermoepidermal junction.

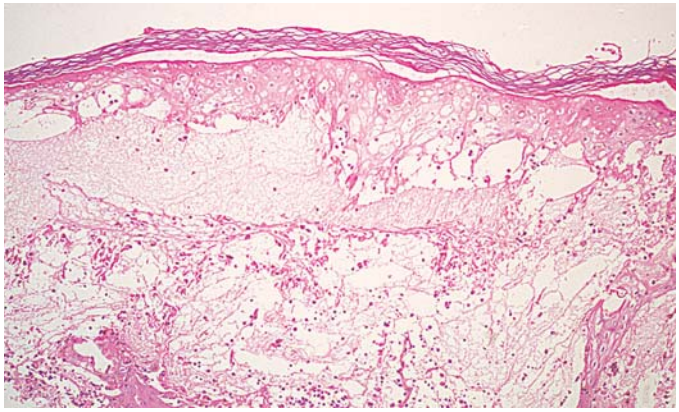

Fig. 12.4: A case of bullous EM showing full-thickness epidermal necrosis with subepidermal accumulation of fibrin and mild chronic inflammation (H & E, ×10).

STEVENS–JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe life-threatening dermatological disorders, characterized by extensive necrosis and detachment of the epidermis and mucosal surfaces.[21,22] Several agents including allopurinol, aromatic anticonvulsants, antibacterial sulfonamides, lamotrigine, nevirapine, and NSAIDs are culprit drugs.[23,24]

Histopathological Features

The hallmark of SJS/TEN is keratinocyte necrosis, ranging from partial to full-thickness necrosis of the epidermis. Early TEN resembles EM, displaying scattered necrotic keratinocytes. Full-thickness epidermal necrosis and a subepidermal split appear in more advanced stages of TEN[25] (Fig. 12.5). The chronic inflammation in papillary dermis decreases in the spectrum from EM to TEN.

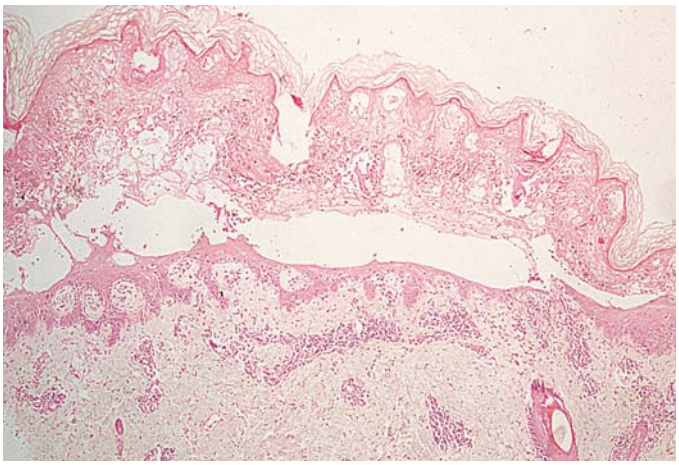

Fig. 12.5: A case of SJS showing full-thickness epidermal necrosis with regeneration of viable epidermis below it and Perivascular lymphocytic infiltrate in upper dermis. Many lymphocytes are tagged to the basal layer of epidermis (H & E, ×4).

Wetter et al.[26] evaluated 15 biopsies from 13 SJS patients, 11 of drug-induced SJS, 2 mycoplasma-induced, and 1 immunization-induced case. Epidermal necrosis was present in 8/13 (62%) patients. Full-thickness epidermal necrosis was seen in six patients (46%). Basal cell damage was observed in 10 (77%) patients and 11 patients (85%) displayed moderate-to-dense dermal infiltrate, with lymphocytic predominance. Eosinophils were present in eight cases, whereas neutrophils were seen in four patients. Other less common findings included regenerating epidermis, parakeratosis, necrosis of the hair follicle, RBC extravasation (5/13 patients), and pigment incontinence. Histologic features such as parakeratosis, individual necrotic keratinocytes, a dense dermal infiltrate of eosinophils or neutrophils, RBC extravasation, and pigment incontinence were present in only drug-induced cases.

SYMMETRICAL DRUG-RELATED INTERTRIGINOUS AND FLEXURAL EXANTHEMA

Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (Baboon syndrome) is a benign, self-limiting disorder characterized by symmetrical erythema involving predominantly flexures, in

the absence of systemic involvement. Important implicated drugs include antibiotics particularly β-lactams, antihypertensives, radiocontrast media, and chemotherapeutic agents.[27]

Histological Features

Histopathological features of SDRIFE are similar to a drug-induced MPE.[27]

DRUG-INDUCED HYPERPIGMENTATION

Drug-induced pigmentation constitutes 10%–20% of all causes of acquired hyperpigmentation.[28] It results either from increased melanin synthesis or due to deposition of the drug or its metabolites.

Minocycline-Induced Pigmentation

Chronic minocycline therapy may result in pigmentation of skin, subcutaneous fat, nails, lips, oral cavity, conjunctiva, and sclera. Three clinical types of cutaneous pigmentation due to minocycline are recognized and are as follows:

Type I: Blue-black/grey pigmentation localized to areas of scarring and inflammation (e.g. facial acne scars)

Type II: (most common type) blue-grey/brown pigmentation on the shins and forearms

Type III: Diffuse muddy-brown discoloration usually on photoexposed sites

A fourth variant affecting the lips and possibly representing a FDE has been described.

Histological Features

The histological features are variable. In clinical types I and II, golden-brown to brown-black granules are seen mainly within the macrophages in perivascular and perieccrine location. There is no increase in melanin or melanocytes. Pigmentation of the subcutaneous fat can also occur in the type II variant in which pigmentation is seen inside macrophages and giant cells in the subcutaneous fat. This pigment shows positive staining for Fontana-Masson and variable staining for iron by Perl's stain. Type III hyperpigmentation is characterized by increased melanin in basal keratinocytes.

Amiodarone-Induced Pigmentation

Long-term therapy with amiodarone leads to characteristic blue-gray discoloration, mostly on the face, ears, and palms.[29]

Histological Features

There are yellow-brown deposits of lipofuscin within macrophages, mast cells, endothelial cells, smooth muscle cells, keratinocytes, and fibroblasts.[29,30]

Quintanilla et al. studied 13 biopsies from 8 patients with amiodarone-induced skin pigmentation, which revealed that pigmentation was due to increase in melanin, solar elastosis, and aggregation of amiodarone in the upper dermis.[31] Amiodarone pigment showed negative staining for fat stains and positive staining for Fontana-Masson stain. The pigment was neither birefringent nor autofluorescent. Ultrastructurally, amiodarone granules appeared as membrane-bound granules with a "fingerprint-like" lamellated structure. The authors concluded that this pigment might be a metabolite of amiodarone, morphologically and histochemically related to melanin.

Other Drugs Causing Cutaneous Pigmentation

Clofazimine

It causes reddish-brown cutaneous and conjunctival pigmentation, which is accentuated in sun–exposed areas but is typically generalized, and nails are often involved. Two types of pigments accumulate in the skin, redox dye and lipofuscin–ceroid. On hematoxylin and eosin (H & E)-stained sections, pigment cannot be demonstrated, although sometimes a light brown deposit may be appreciated within foamy histiocytes in leprosy cases. On fresh frozen sections, birefringent red clofazimine crystals concentrated around larger dermal vessels can be seen. They appear deep red on fluorescence microscopy. However, both the redox dye and lipofuscin do not stain with acid fast, melanin, or iron stains. Lipofuscin–ceroid is identified by Mallory's hemofuscin stain in paraffin-embedded sections.[32]

Antimalarials

Antimalarials (i.e. chloroquine, hydroxychloroquine, and quinacrine) can induce tissue pigmentation of skin, joints, trachea, and cartilages. In SLE patients treated with antimalarials, the incidence of cutaneous hyperpigmentation is 10%–25%.[33] Jallouli et al. observed brown pigmented granules in macrophages and fibroblasts in both perivascular and interstitial location in the dermis and subcutis in SLE cases on hydroxychloroquine.[33] It stained strongly with Perl's stain, suggesting presence of iron. Fontana-Masson stain was also found to staining positively to some of these granules, suggesting the presence of melanin. There was also increased epidermal melanin.

Chlorpromazine

Histologically, chlorpromazine-induced pigmentation is characterized by golden-brown macrophage-bound

granules in perivascular location in superficial dermis. These granules show positive staining with Fontana-Masson but not with Perl's stain. Increased epidermal melanin is also seen, which also contributes to chlorpromazine-induced cutaneous pigmentation.

Tricyclic Antidepressants

Imipramine and desipramine hyperpigmentation histologically demonstrates golden-brown granules within macrophages as well as lying freely in upper dermis. These granules show positive staining with Masson-Fontana, whereas Perl's staining is negative.

VASCULITIC DRUG REACTIONS

Drug-induced vasculitis may be an adverse event of various drugs such as anti-infective or chemotherapeutic agents, cardiovascular drugs, diuretics, anticoagulants, β-adrenergic receptor agonists, anticonvulsants, and anti-tumor necrosis factor (TNF)-α therapies. Granulomatous vasculitic drug reaction has been reported with allopurinol, chlorothiazide, phenytoin, and carbamazepine.

Histological Features

Histology shows features of leukocytoclastic vasculitis of small caliber vessels with increased number of eosinophils. In fact, a predominant perivascular eosinophilic infiltrate may be seen in nondrug-induced vasculitis, which makes differentiation from drug-induced vasculitis difficult and a clinicopathological correlation is required. Drug-induced vasculitis is uncommonly granulomatous.[11]

Bahramiet al. evaluated biopsies of 16 drug-induced and 47 nondrug-induced cutaneous small vessel vasculitis cases.[34] Significant difference was seen only in mean eosinophil infiltrate in drug-induced versus nondrug-induced cases.

PUSTULAR DRUG REACTIONS

AGEP is an uncommon dermatoses characterized by superficial pustules. It is characterized by acute onset development of multiple small, nonfollicular pustules on erythematous base, associated with pruritus, often morphologically indistinguishable from pustular psoriasis. The eruption commonly starts on the face or intertriginous regions and rapidly involves other body sites and becomes generalized. AGEP is caused by drugs in approximately 80%–90% cases.[35,36]

Histological Features

It is characterized by intra- and subcorneal neutrophilic collection along with spongiform pustules of Kogoj, similar to pustular psoriasis. There is papillary dermal edema and neutrophils and eosinophils (Fig.12.6 a and b). An increased number of dermal eosinophils may differentiate AGEP from pustular psoriasis, although this feature may also be present in the latter.

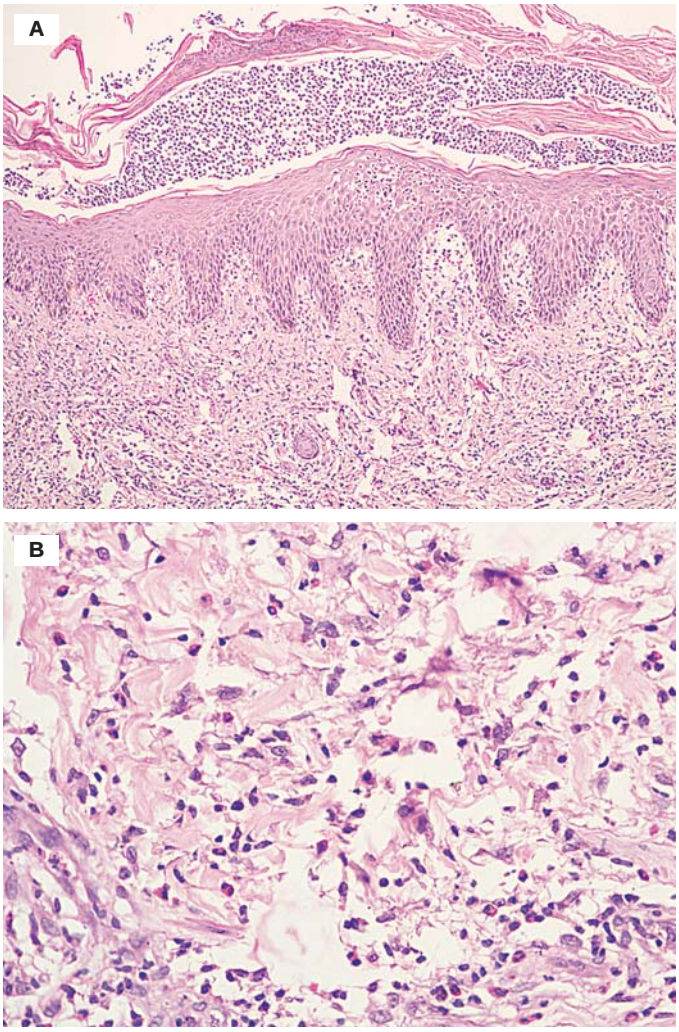

Fig. 12.6: (A) A case of AGEP showing parakeratosis, subcorneal neutrophilic abscess, and spongiform pustule in the epidermis. Irregular acanthosis, upper dermal inflammatory infiltrate, and edema in dermal papilla (H & E, ×10); (B) A case of AGEP showing many eosinophils admixed with lymphocytes in papillary dermis (H & E, ×40).

A retrospective histopathological study on 102 AGEP cases showed sub/intracorneal pustules and intraepidermal pustules in 41% and 20% cases, respectively, whereas combinations of both were seen in 38% cases.[37] The pustules were usually large covering >15 keratinocytes and also contained eosinophils (in sub/intracorneal location in 36% and intraepidermal location in 32% cases). Other features were necrotic keratinocytes (67%), spongiosis (80%) with neutrophil exocytosis (77%), and papillary

dermal edema (88%). Mixed infiltrate containing neutrophils (100%) and eosinophils (81%) were seen in all locations of dermis. Follicular pustules were also observed in 23% cases.

GRANULOMATOUS DRUG REACTIONS

Interstitial granulomatous drug reactions are characterized by pruritic, irregular, and sometimes annular violaceous papules and plaques predominantly in skin fold areas. Commonly associated drugs include antihypertensives, antihistamines, anticonvulsants, antidepressants, lipid-lowering agents, and NSAIDs.[38,39]

Histological Features

There is interstitial mixed cell infiltrate consisting of lymphocytes, histiocytes, eosinophils, plasma cells, and multinucleate giant cells. Sometimes, it can be associated with increased dermal mucin. Elastophagocytosis may be present. This may be associated with interface dermatitis also involving the hair follicles and acrosyringium.[38] Churg–Strauss-like granulomata and flame figures can also be seen.[39] There may be epidermotropism of atypical lymphocytes mimicking mycosis fungoides.[38]

BULLOUS DRUG REACTIONS

Development of blisters following drug administration occurs as a consequence of marked spongiosis and/or prominent interface change.

Drug-Induced Pemphigus

Drug-induced pemphigus can be induced or triggered by penicillamine, captopril, rifampicin, etc. Clinically, it can resemble pemphigus foliaceous, vulgaris, or erythematosus. Clues to the diagnosis include pruritus, a prodromal rash, and absence of mucosal involvement.

Histological Features

Histologically, there is no difference between drug-induced and idiopathic variants. Direct (DIF) and indirect immunofluorescence (IIF) studies may be negative in some patients. In a series of six drug-induced pemphigus cases, DIF was negative in one and IIF in two patients. Enzyme-linked immunosorbent assay (ELISA) was positive for desmoglein 1 or desmoglein 3 in all patients in this series.[40]

Drug-Induced Bullous Pemphigoid

Drug-induced bullous pemphigoid (BP) is characterized by a younger age of onset than the spontaneously occurring BP. Various drugs including captopril, penicillamine, chloroquine, furosemide, spironolactone, NSAIDs, sulfasalazine, ciprofloxacin, and enoxaparin have been incriminated. Clinically, lesions are difficult to distinguish from idiopathic BP. They may be accompanied by EM type of lesions on palms and soles.[41]

Histological Features

Histologically, drug-induced variants are almost similar to typical BP with subtle differences that include intraepidermal blister with necrotic keratinocytes.[42] The typical histological features include subepidermal blisters containing numerous eosinophils sometimes admixed with neutrophils and fibrin. The findings on DIF and IIF are similar to those of classic BP.[41]

Drug-Induced Epidermolysis Bullosa Acquisita

It has been reported following treatment with vancomycin, penicillamine, and granulocyte–macrophage colony–stimulating factor (GM-CSF).

Histological Features

Histopathology is similar to the idiopathic variant and shows the presence of a subepidermal blister containing mixed inflammatory cell infiltrate. DIF reveals a thick linear band of IgG, and to a lesser extent C3 and IgM at the basement membrane zone, similar to conventional epidermolysis bullosa acquisita (EBA) and salt split technique detects circulating IgG autoantibodies that bind to the dermal side (floor) of the blister.[43]

Drug-Induced Linear Iga Disease

Vancomycin is the commonest drug associated with this entity. Other drugs implicated include phenytoin, lithium, amiodarone, captopril, β-lactam antibiotics, trimethoprim–sulfamethoxazole, cyclosporine, NSAIDs, interleukins, and interferons. Cutaneous manifestations of drug-induced linear IgA disease are almost similar to the idiopathic form.

Histological Features

These are indistinguishable from the idiopathic form with presence of subepidermal cleft, which is neutrophil rich or admixed with eosinophils. Few features such as eosinophils being the predominant cell type and focal necrotic keratinocytes arranged near the basal membrane may point toward drug-induced linear IgA dermatosis (LAD), but a clinicopathological correlation is required. Similar to classic LAD, DIF exhibits a pure linear deposition

of IgA along the basement membrane zone with or without fibrinogen.[44]

Drug-Induced Pseudoporphyria

Pseudoporphyria is a photodistributed disorder with clinical and histologic features similar to porphyria cutanea tarda (PCT), but without any biochemical porphyrin abnormalities. Medications like diuretics such as furosemide and NSAIDs, particularly naproxen, are implicated.[45]

Histological Features

The histologic features closely resemble those of PCT with a non-inflammatory subepidermal blister and a scant perivascular lymphocytic infiltrate. Similar to PCT, there is preservation of the dermal papillae (festooning) and accumulation of PAS-positive eosinophilic hyalinized material around the upper dermal vessels. However, the thickened blood vessels may help to distinguish PCT from pseudoporphyria as it is observed in the former.[46] Solar elastosis that is generally evident in PCT may not be seen in drug-induced pseudoporphyria.[47] Immunoglobulins, most commonly IgG, are seen at the dermoepidermal junction, and around the superficial dermal vessels.[48]

PSORIASIFORM DRUG REACTIONS

Psoriasiform dermatoses can be caused by lithium, β-blockers, NSAIDs, synthetic antimalarials, tetracyclines, and TNF-α inhibitors. Drug-induced psoriasiform reactions appear very similar to idiopathic psoriasis.

Histological Features

It reveals many features similar to classic psoriasis. There is psoriasiform epidermal hyperplasia, neutrophils within parakeratotic stratum corneum, hypogranulosis, and superficial perivascular lymphocytes, histiocytes, and eosinophils. There may be some interface dermatitis. A helpful feature distinguishing drug-induced psoriasis from idiopathic psoriasis is the absence of tortuous papillary dermal capillaries and suprapapillary epidermal thinning.[11] TNF-α inhibitors may also demonstrate spongiosis and lichenoid interface change.

PITYRIASIFORM DRUG REACTIONS

Patients present as pityriasis rosea, although the herald patch of classic pityriasis rosea is usually absent in drug-induced cases. Pityriasiform drug reactions have been reported with various drugs including ACE inhibitors, NSAIDs, gold, terbinafine, barbiturates, isotretinoin, and imatinib.

Histological Features

These are similar to idiopathic pityriasis rosea including mounds of parakeratosis, focal spongiosis, mild epidermal hyperplasia, focal basal cell vacuolar change, and a superficial perivascular infiltrate of lymphocytes and sometimes eosinophils.[49]

ICHTHYOSIFORM DRUG REACTIONS

Acquired ichthyosis occurs following use of lipid-lowering agents, nicotinic acid, targeted cancer therapy [e.g. vemurafenib, epidermal growth factor receptor (EGFR), and protein kinase inhibitors.] and kava (psychoactive beverage prepared from the root of the pepper plant). The clinical and histological features resemble ichthyosis vulgaris or lamellar ichthyosis.

DRUG-INDUCED PSEUDOLYMPHOMA

These are benign lymphoproliferative processes that resemble lymphoma clinically and histologically and usually occur months to years after drug initiation. Lymphomatoid drug eruptions are commonly T cell type. Important implicated drugs include anticonvulsants, antihypertensives, NSAIDs, sedatives, and antidepressants.

Histological Features

Mycosis fungoides (MF)-like pseudolymphomas are the most frequent. Similar to classic MF, it presents as a dense superficial infiltrate in perivascular location or band-like infiltrate consisting of lymphocytes, histiocytes including atypical lymphocytes with irregular, enlarged, cerebriform hyperchromatic nuclei and associated epidermotropism. Pautrier's microabscesses can also be identified. However, eosinophils are frequently present and the epidermis shows significant spongiosis. There may be a polymorphous infiltrate in the deep perivascular or periadnexal locations. Giant cells and epithelioid granulomata may also be seen.[50] Nodular drug-induced cutaneous T cell pseudolymphomas (CTPLs) may occur independently or coexist with MF-like lesions. The infiltrate demonstrates polymorphous nodular infiltrate of small lymphocytes with none-to-mild atypia, admixed with histiocytes, plasma cells, and eosinophils.[50] Studies have disclosed a clonal population of lymphocytes on T cell receptor gene rearrangement in only a minority of patients.

B cell lymphomatoid drug reaction is characterized by a diffuse pandermal or nodular, often polymorphous infiltrate of lymphocytes, histiocytes, plasma cells, and eosinophils, with extension into the subcutaneous fat. Lymphoid follicles with germinal centers may be evident and mitoses are sometimes numerous.

DRUG-INDUCED PANNICULITIS

It occurs due to direct injection of certain drugs (apomorphine, glatiramer etc.), withdrawal of corticosteroids or as a systemic drug-induced effect (thiazides, sulfonamides, corticosteroids, oral contraceptives, and chemotherapeutic agents). Erythema nodosum is the commonest drug-induced panniculitis.

Histological Features

Erythema nodosum manifests as septal panniculitis without vasculitis with septal edema and thickening, with mixed lymphohistiocytic and neutrophil/eosinophil infiltrate in the septa. Multinucleated giant cells are present in late stage.

Drug-induced panniculitis occurs in cancer patients, especially chronic myelogenous leukemia patients receiving tyrosine kinase antagonists such as imatinib and dasatinib. It manifests as a lobular panniculitis with mixed cell infiltrate (imatinib), whereas neutrophilic predominance is seen with dasatinib. All-trans retinoic acid have been reported to cause neutrophilic lobular panniculitis.[51]

PURPURIC DRUG REACTIONS

Purpura may occur following use of NSAIDs, diuretics, meprobamate, ampicillin, pseudoephedrine, linezolid, and lidocaine/prilocaine cream. These cause purpura simplex (PS)-like lesions, manifesting as hemorrhage, dermatitis, and pigmentation. Lesions of drug-induced PS are significantly more generalized as compared to idiopathic PS.[52]

Histological Features

This includes RBC extravasation and a mild perivascular inflammation without fibrinoid necrosis.[52]

DRUG-INDUCED LUPUS ERYTHEMATOSUS

It has been reported following administration of hydralazine, isoniazid, procainamide, sulfa drugs, penicillamine, quinidine, methyldopa, carbamazepine, captopril, minocycline, and TNF-α inhibitors.

Histological Features

The histological features are those of classic LE.

SPECIFIC DRUG REACTIONS

Arsenic

Exposure to arsenic may lead to acute arsenical dermatitis or chronic arsenism, resulting in pigmentary disturbances and cutaneous tumors.

There is characteristic "rain drop" pigmentation, seen on the trunk and in pigmented regions of body such as areola and flexures. Skin tumors [basal cell carcinoma, Bowen's disease, and squamous cell carcinoma (SCC)], which are often multiple and particularly found on sun-protected sites, and punctate palmoplantar keratoderma are seen.

Histological Features

Cutaneous hyperpigmentation demonstrates increased melanin both in basal and suprabasal layers without evidence of melanocytic proliferation. Skin cancers histologically show no distinguishing features from those developing due to other causes.

Iododerma

Exposure to potassium iodide in expectorants/bronchodilators, during treatment of thyroid disease and as a radiocontrast medium, may cause acneiform papulo/pustular lesions, which affects face, neck, and back. Uncommonly, urticarial, vesiculobullous, and pustular psoriasis-like lesions can be seen. Nodular and ulcerated vegetative plaques affecting the face, shoulders, trunk, and extremities may be grotesque manifestation.

Histological Features

Acute lesions show a dense infiltrate of neutrophils in the dermis. Pseudoepitheliomatous hyperplasia and ulceration are commonly seen in chronic lesions. Neutrophilic, occasionally eosinophilic, microabscesses can be seen in the epidermis. In some cases, focal leukocytoclastic vasculitis may be observed.

Bromoderma

Methyl bromide exposure via pesticides, disinfectants, sedative syrups, expectorants, film, and dye industries produces the condition. Lesions vary from sharply circumscribed erythematous vesiculobullous lesions to urticaria, acneiform/pustular lesions, ulcerated vegetative plaques, necrotizing panniculitis, and pyoderma gangrenosum-like ulcers.

Histological Features

Acute lesions are characterized by spongiosis, necrotic keratinocytes, and papillary dermal edema along with a superficial perivascular mixed cell infiltrate. Vegetative lesions show marked pseudoepitheliomatous hyperplasia with intraepidermal abscesses. Urticarial lesions show papillary dermal edema and perivascular neutrophil- and eosinophil-rich infiltrate.

Warfarin-Induced Cutaneous Necrosis

Cutaneous necrosis develops in 0.01%–0.1% cases, 3–6 days after starting anticoagulant therapy. Most common sites affected are the breasts, buttocks, and thighs. Initial paresthesia is followed by development of painful, well-defined, edematous, and erythematous plaque resembling peau d'orange with purpura. This is followed by large hemorrhagic bullae, which break down rapidly and progress to necrosis of the dermis and subcutis.

Histological Features

There are fibrin thrombi within small veins and venules of the dermis and subcutis, with extensive RBC extravasation and subepidermal hemorrhagic blisters in advanced lesions. Ischemic necrosis of overlying epidermis is present. Vasculitis is not a feature. Arteries are not affected.

Rarely, heparin can lead to paradoxical thrombosis and skin necrosis. Heparin-induced cutaneous necrosis is characterized by similar features of vasculopathy.

Penicillamine

D-penicillamine interferes with collagen and elastin cross-linking and produces several cutaneous side effects. Long-term administration of D-penicillamine causes dermopathy in 20%–33% of patients.

Histological Features

Elastic fiber damage due to penicillamine presents as thickening and fragmentation of elastic fibers with prominent lateral protrusion, which gives the characteristic "bramble-bush" appearance. Fragmented elastic fiber can become calcified and is sometimes associated with granulomatous inflammation. Transepidermal elimination of elastic fibers is seen in elastosis perforans serpiginosa.[53]

Gold

Gold therapy may lead to lichenoid, eczematous, psoriasiform, and pityriasiform dermatoses following parenteral treatment (chrysiasis). It is a photodependent, irreversible condition in patients who have attained a threshold of 50mg/kg of gold.

Histologic Features

It is characterized by deposits of small black particles in macrophages in perivascular and perieccrine location in the upper and mid dermis. Perl's stain and Masson-Fontana are negative. There is no inflammatory infiltrate. Gold particles show a striking orange-red birefringence under polarized light.

Silver

Chronic exposure to chemical compounds containing silver leads to argyria. It presents as gray to gray-black pigmentation of the skin and mucous membranes. The hyperpigmentation is most prominent over sun-exposed areas.

Histologically, small, brown-black granules appear singly or in close aggregates around sweat glands, in the connective tissue sheath around the pilosebaceous structures, arrector pili muscles, arteriolar walls, and nerves. They have a predilection for elastic fibers. They appear refractile on dark-field illumination, which gives a "stars in heaven" pattern.

Chemotherapeutic Agents

Newer chemotherapeutic agents that selectively target specific cellular pathways produce diverse cutaneous side effects. EGFR inhibitors (panitumumab, necitumumab cetuximab, gefitinib, and erlotinib) produce adverse effects on the skin and appendages due to expression of EGFR on these structures.

Papulopustular Eruption

It is the most frequent side effect. The follicular papules and pustules are usually present in seborrheic distribution. Comedones are uncommon finding.

Histopathological Features

There is involvement of the epidermis (52%), hair follicles (61%), and sebaceous glands (45%).[54] Superficial perifolliculitis and florid neutrophilic suppurative folliculitis are the two major histopathologic patterns. Superficial perifolliculitis is characterized by neutrophilic infiltrate around the dilated and plugged follicular infundibula, whereas florid neutrophilic suppurative folliculitis presents with rupture of the follicular epithelium and subsequent perifollicular granuloma formation. Intraepidermal acantholysis in sweat ducts, dyskeratotic keratinocytes, lichenoid infiltrate, and sebaceous gland hypoplasia are other features.[55–61]

Xerosis

Xerosis is observed in 12%–35% patients receiving EGFR inhibitors. Histologically, the epidermis is atrophic with hyperparakeratosis.[55]

Paronychia

Paronychia occurs in 10%–15% of patients treated with cetuximab and gefitinib.[56]

Histopathological Features

It shows marked dermal edema and inflammation consisting of plasma cells, lymphocytes, and neutrophils. Endothelial swelling of vessels is present. There is no evidence of Candida, other fungi, or bacteria on cultures.[56]

Tyrosine Kinase Inhibitors

Tyrosine kinase inhibitors (TKIs) (imatinib, sorafenib, sunitinib, gefitinib, erlotinib, and dasatinib) produce various skin eruptions such as exanthematous papular eruption, superficial edema, pigmentary changes, SJS/TEN, AGEP, Sweet's syndrome, photosensitization, psoriasiform eruptions, and exacerbations of psoriasis, hand–foot skin reaction (HFSR), and squamoproliferative lesions.

Hand–Foot Skin Reaction

HFSR presents as symmetrical painful erythematous areas over the palms and soles including the lateral sides of fingers and periungual areas. It is preceded by tingling sensation and intolerance to hot objects, with patients experiencing difficulty in walking and holding objects. Sorafenib and sunitinib are most commonly implicated drugs.

Histological Findings

These include parakeratosis and dyskeratosis with band-like areas of necrotic keratinocytes.[57] Lacouture et al.[58] analyzed seven biopsies of HFSR and found band-like areas of necrotic keratinocytes in all patients, two being associated with blistering and abnormalities in the stratum corneum with hyperparakeratosis in five patients (biopsies obtained at ≥30 days). Superficial telangiectasia and a mild perivascular lymphohistiocytic infiltrate were present in all biopsies. Dysmorphic eccrine cells with scant cytoplasm and cystic changes can be observed in sweat glands.

Squamoproliferative Lesions

Treatment with sorafenib can lead to the development of actinic keratosis, keratoacanthomas (KA), and SCCs within 2 weeks to 3 years after initiating therapy.[59,60] Spontaneous regression of KAs has been reported after discontinuation of the drug, and also in a few patients who continued therapy. Histopathology is similar to classic KA or SCC.

Neutrophilic Eccrine Hidradenitis

It occurs in association with malignancy (with or without chemotherapy), infections, and certain medications. Most cases are those of acute myelogenous leukemia undergoing chemotherapy with cytarabine. It presents as erythematous tender plaques, nodules, papules, and pustules and edematous, hemorrhagic, purpuric, and cellulitis-like lesions.

Histological Features

There is a dense neutrophilic infiltrate around and within the eccrine glands, associated with vacuolar degeneration and even necrosis of the secretory epithelium. The neutrophilic infiltrate can be observed around and within the eccrine ducts, usually sparing the acrosyringium. The infiltrate is mild in neutropenic patients.[61,62] There may be edema and mucin deposition in the loose connective tissue and fat surrounding the coils. Rarely, apocrine gland involvement can be seen.[63] Other features include a lichenoid tissue reaction with prominent basal cell damage in some cases, squamous syringometaplasia, dermal hemorrhage, dermal edema, epidermal spongiosis, focal keratinocyte necrosis, mucin deposition, and mild panniculitis.

Shih et al.[64] assessed the immunohistological features of 10 cases of childhood neutrophilic eccrine hidradenitis. All biopsy specimens showed neutrophilic infiltrates around perieccrine and perivascular location with no leukocytoclastic vasculitis.[64]

LEARNING ESSENTIALS

- A strong temporal correlation between the cutaneous adverse reaction and drug administration, reproducibility of the reaction upon drug rechallenge, and resolution of the eruption on cessation of therapy are the key elements in implicating a drug in the causality of a reaction.
- Ethical issues associated with drug provocation tests and little significance of the in vitro and in vivo tests prompt the treating physician to undertake a skin biopsy.
- Histology of drug reactions may be very specific, may provide important clues to the diagnosis of a drug eruption, or evoke a range of overlapping reaction patterns not representative to a particular disease that warrants a clinicopathologic correlation.
- A skin biopsy undertaken at an appropriate time during the evolution of a drug rash may provide meaningful information to the dermatologist and would be an important pharmacodiagnostic tool in his armamentarium.

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Chapter

13

Fixed Drug Eruption

Lalit Kumar Gupta • Manisha Balai • Ashok Kumar Khare

SUMMARY

Fixed drug eruption (FDE) is one of the most specific mucocutaneous reaction pattern induced by drug(s). The lesions characteristically recur at the same site following re-exposure to the drug. In active stage, the disease is usually characterized by a few circumscribed, dusky red oval or round macules or plaques. The diagnosis is easy even when the lesions have healed, on account of characteristic residual pigmentation. Unusual morphological variants, however, are increasingly recognized, thereby expanding the clinical spectrum of FDE. The drugs commonly precipitating FDE include nonsteroidal anti-inflammatory drugs (NSAIDs) and antibiotics. FDE is mediated by skin-resident $CD8^+$ T cells belonging to effector-memory phenotype that can specifically recognize drug antigen. The incriminating drug causing FDE can be confirmed by provocation test, both oral and patch testing at the lesional site.

INTRODUCTION

Fixed drug eruption (FDE) is a common adverse cutaneous reaction pattern to medications. It was first described by Bourns.[1] The term FDE was coined by Brocq[2] to describe a pattern of skin eruption to antipyrine. The hallmark of the disease is the occurrence of lesion(s) at the same site each time following administration of the causative drug(s) and the characteristic residual hyperpigmentation upon healing.[3] The drugs causing FDE differ from region to region and keep changing depending on the prescription pattern and health attitude of patients.[4] There is no specific age and sex predilection in FDE.[5] Although FDE is sporadic, familial occurrence has been reported.[6,7] The risk of developing FDE has been linked to certain human leukocyte antigen (HLA) haplotypes. These include HLA-B22 and HLA-A30 in febrazone and trimethoprim-sulfamethoxazole induced FDE respectively.[8,9]

CLINICAL FEATURES

Although clinical diagnosis of FDE is usually easy and straightforward, unusual and atypical presentations of the disease may at times cause diagnostic confusion. A typical FDE lesion is a well-demarcated, round or oval, bright to dull red macule ranging from several millimeters to over 10 cm in diameter on skin and/or mucosa (Figs. 13.1A and B).[10] Usually, a solitary lesion or a few lesions are present. As the lesions evolve, they may develop into edema with dark bluish or purple center (Fig. 13.2). Vesicles or even blisters can develop if the inflammation is marked (Figs. 13.1A and 13.3). The halo of erythema around dark central area may be prominently present even in dark skin.[5] The lesions often heal with residual hyperpigmentation (Fig. 13.4), a characteristic feature of the disease.[3] The shade of hyperpigmentation gets darker with each subsequent exposure to the drug. This tendency is more prominent in darker skin type.[11] This characteristic residual pigmentation is absent in the so-called nonpigmenting variant of FDE (NPFDE), leading to diagnostic error.[12] The lesions may be asymptomatic or may be accompanied by burning pain or pruritus. Constitutional symptoms such as fever, nausea, diarrhea, dysuria, and abdominal cramps are rare in typical cases but may be present if the lesions are extensive such as in generalized bullous FDE (GBFDE).[13,14]

FDE has predilection for areas with thin skin, such as the lips (Figs. 13.5 A–C), genitalia 'especially male genitalia (Fig. 13.6), and perianal regions, but the lesions may appear on any area of the skin, mucosa, or mucocutaneous junction.[5] The patients with genital FDE may present in the sexually transmitted

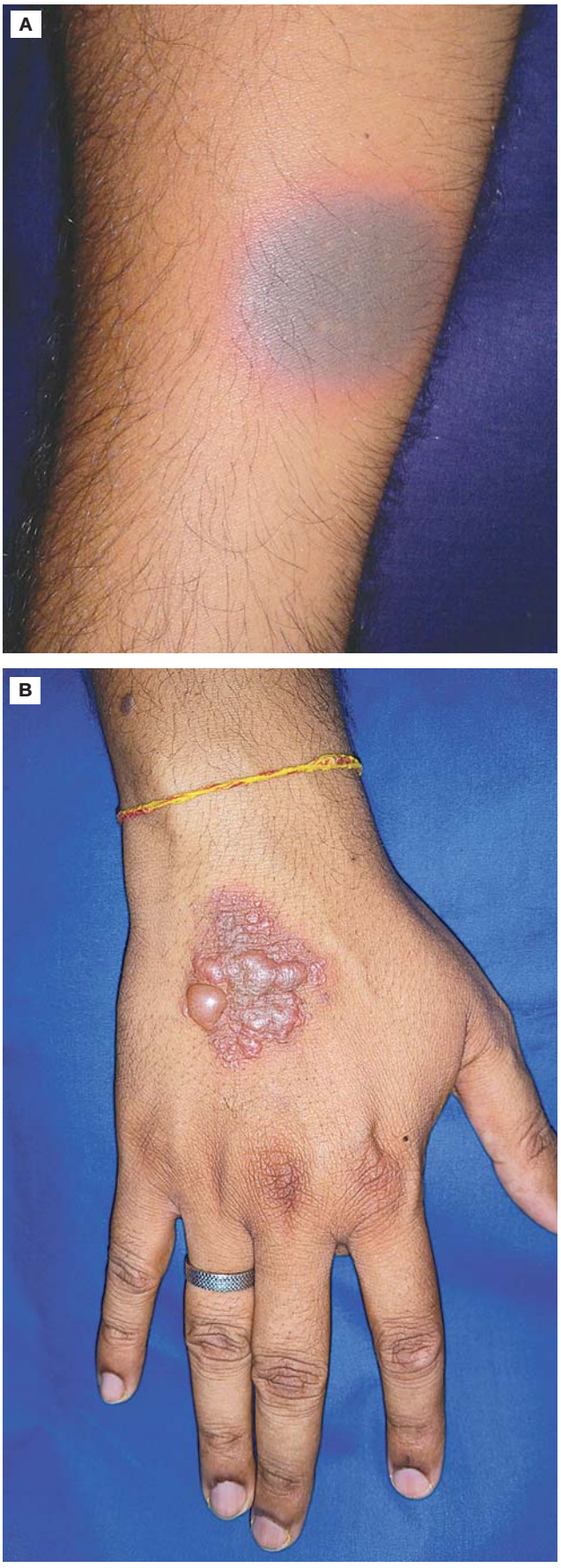

Fig. 13.1: (A & B) Typical, solitary lesions of FDE due to ofloxacin. Note the vesicular change in lesion on hand (B).

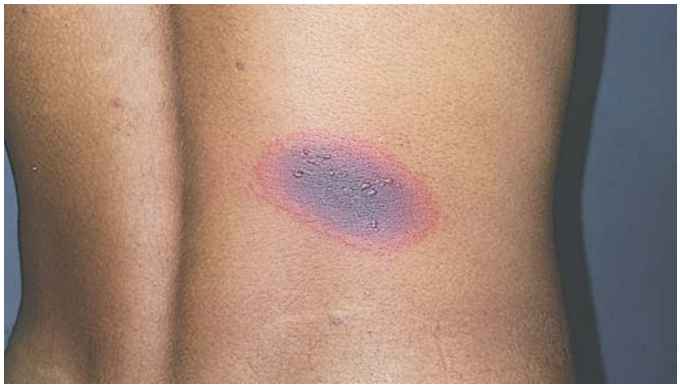

Fig. 13.2: FDE on trunk with prominent erythematous halo. Diclofenac was the suspected cause.

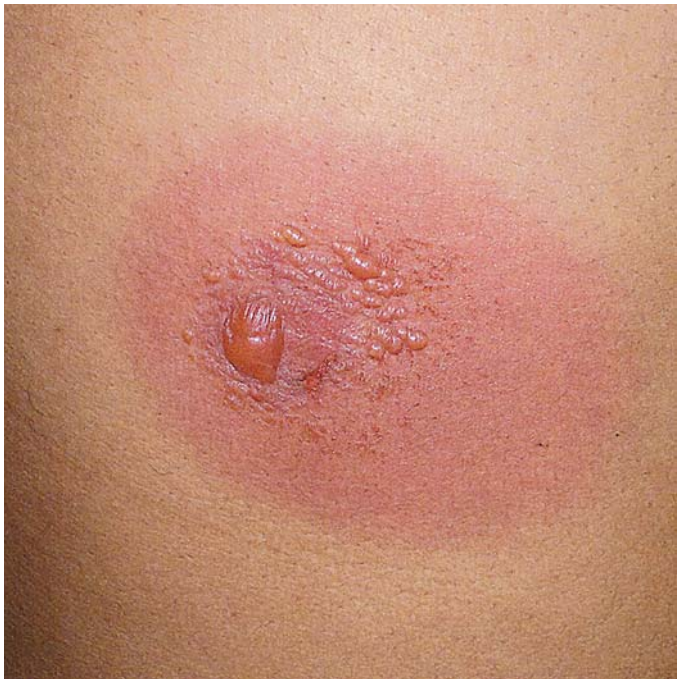

Fig. 13.3: First episode of FDE, with lesion on abdomen 5 days following intake of ornidazole. Note the vesicular change and lack of background hyperpigmentation.

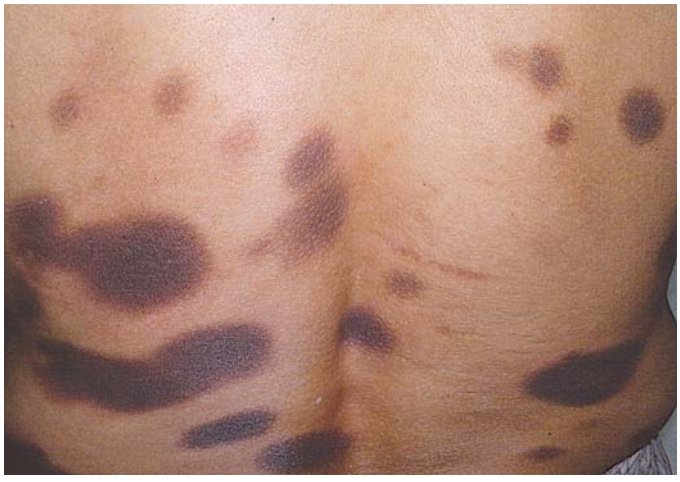

Fig. 13.4: Intense post-inflammatory pigmentation after healing, characteristic of FDE.

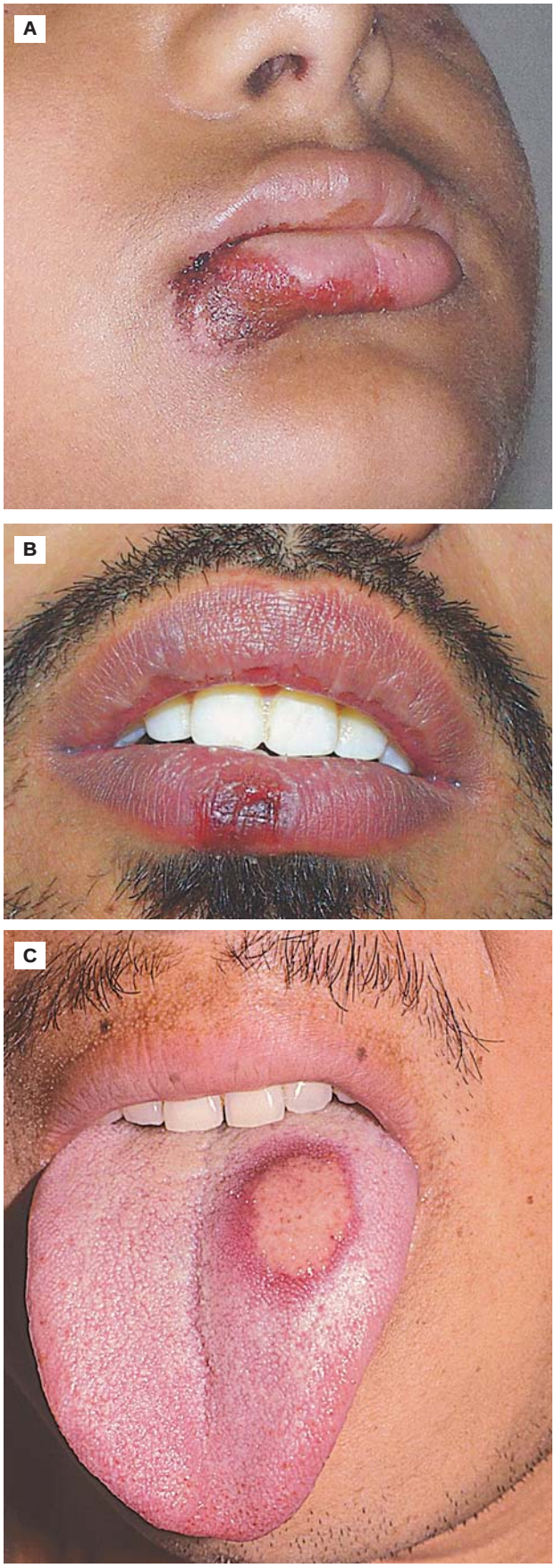

Fig. 13.5: (A–C) FDE affecting angle of mouth, lips and tongue. (Fig. 13.5C; Courtesy of Dr. M. Ramam, New Delhi.)

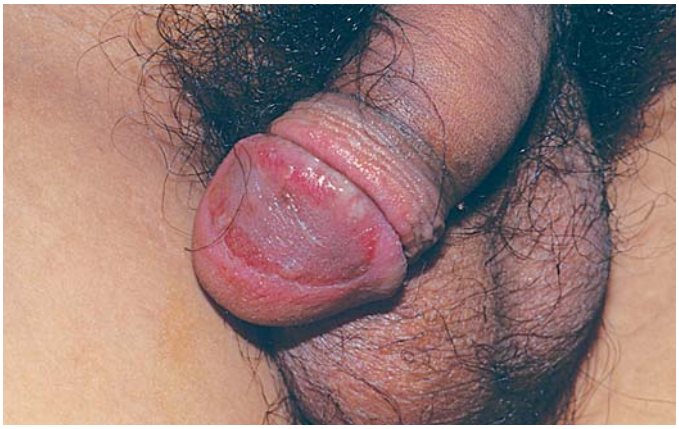

Fig. 13.6: Typical lesion of FDE on glans penis. Co-trimoxazole was suspected as the cause. (Courtesy of Dr. M. Ramam, New Delhi.)

disease (STD) clinics and represent 2% of all genital ulcers.[15] In males, the lesions are usually unifocal and affect glans or shaft of penis. In females, FDE of the vulva manifests as erosive vulvitis with lesions presenting symmetrically on the labia minora and majora and extending to the perineum.[15] In a series of 105 cases of FDE, a correlation between the site of predilection and the offending drug was made, with co-trimoxazole commonly causing lesions on the genital mucosa, naproxen, and oxicams on the lips, and dipyrone on the trunk and extremities.[16]

The first appearance of FDE in a susceptible person depends on the sensitization. Such sensitization occurs more rapidly in patients intermittently consuming the causative drug rather than those receiving them continuously. The period of sensitization varies in each patient and ranges from a few weeks to several years.[17] With subsequent exposure to the same drug, the lesions can develop within minutes up to several hours.[7] The lesions may become more numerous and severe unless the culprit drug is withdrawn. In some patients, despite the continued administration of causative drug, the pigmented lesions disappear due to spontaneous desensitization to the offending drug. This desensitization protocol has been reported to be a successful treatment option of FDE to allopurinol.[18] Although the lesions generally tend to recur at the site of previously healed lesions, exhibiting "recall phenomenon" and hence the name "fixed," some FDE lesions fail to recur despite rechallenge with the culprit drug. This is known as "refractory period," the duration of which may last from several weeks to months.[19]

ROLE OF TRIGGERING FACTORS IN FDE

New lesions often occur at the site of previously inflamed or traumatized skin such as insect bites, burn, and venepuncture.[20] Nonspecific factors such as psyche, emotions, heat, menstruation

abnormalities, pregnancy, cold, and fatigue are found to be responsible for recurrence of FDE.[21] It has also been reported after exposure to ultraviolet radiation.[22]

UNUSUAL FORMS OF FDE

The clinical picture of classical FDE is characteristic. However, the unusual and atypical presentations are being increasingly recognized (Box 13.1).

Box 13.1: Unusual Forms of FDE

- Nonpigmenting
- Generalized bullous
- Inverse
- Linear
- Wandering
- Chronic
- Cellulitis like
- Psoriasiform
- Neutrophilic
- Erythema dyschromicum perstans like
- FDE with pigmentary loss
- Paronychia

Nonpigmenting FDE

The entity was first described by Shelley and Shelley[12] as a variant of FDE in which the residual pigmentation characteristic of classic FDE is not seen (Figs. 13.7A & B).[11] This is a distinctive pattern of FDE and has two variants. The pseudocellulitis or scarlatiniform type is characterized by large, tender, erythematous plaques. Systemic manifestations are usually present. The lesions slowly fade over 2–3 weeks and do not leave behind any residue. Pseudoephedrine is the most common drug inciting this reaction pattern. The second variant is symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), formerly called as baboon syndrome and which presents as erythematous, well-defined fixed plaques usually affecting the buttocks, groin, and axilla.[14] The site of pathology is believed to be dermal rather than epidermal and histologically dermal melanophages, as seen in the classical pigmented variant of FDE, are absent.[11]

Generalized Bullous FDE

A rare variant thought to represent the severe end of the FDE spectrum (Figs. 13.8 A & B) or an abortive variant of the toxic epidermal necrolysis (TEN). Some authors have even suggested that TEN/Steven–Johnson syndrome (SJS) may represent the severe form of bullous FDE on account of their close

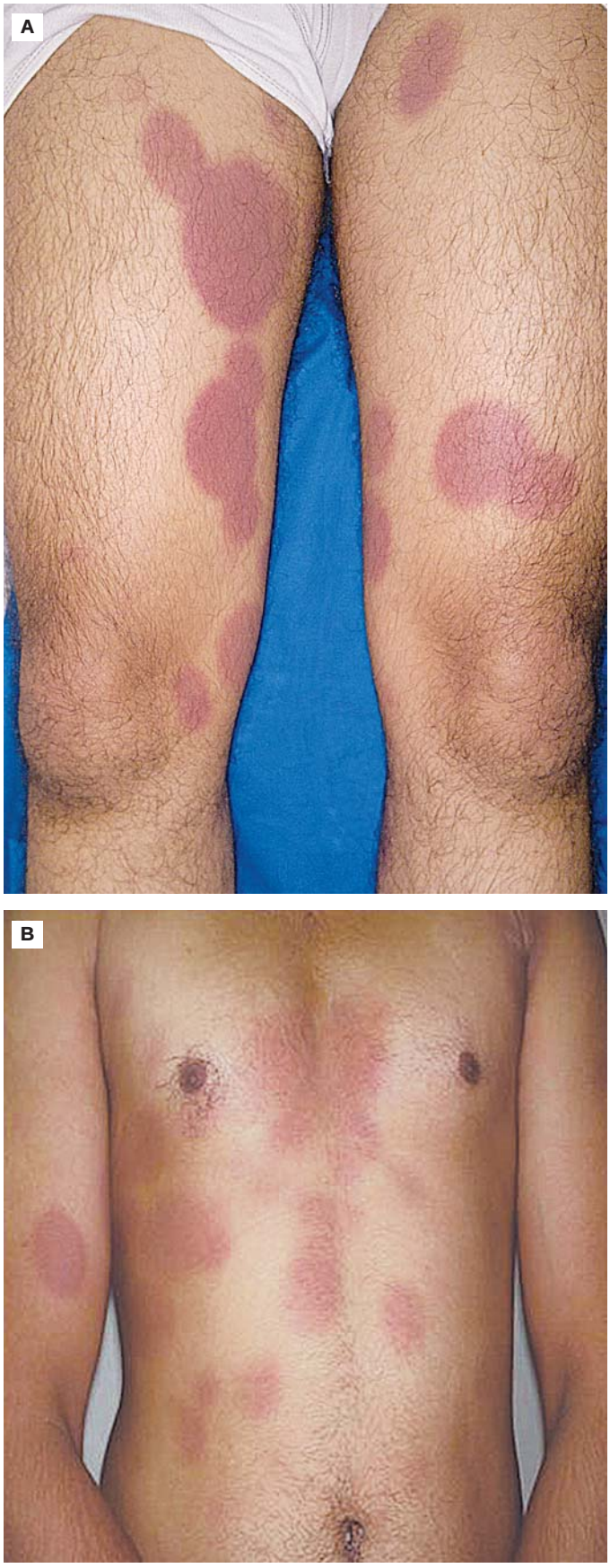

Fig. 13.7: (A & B) Non-pigmentary FDE from fixed combination of ofloxacin and ornidazole. This was the 4th episode. Note the absence of any background hyperpigmentation.

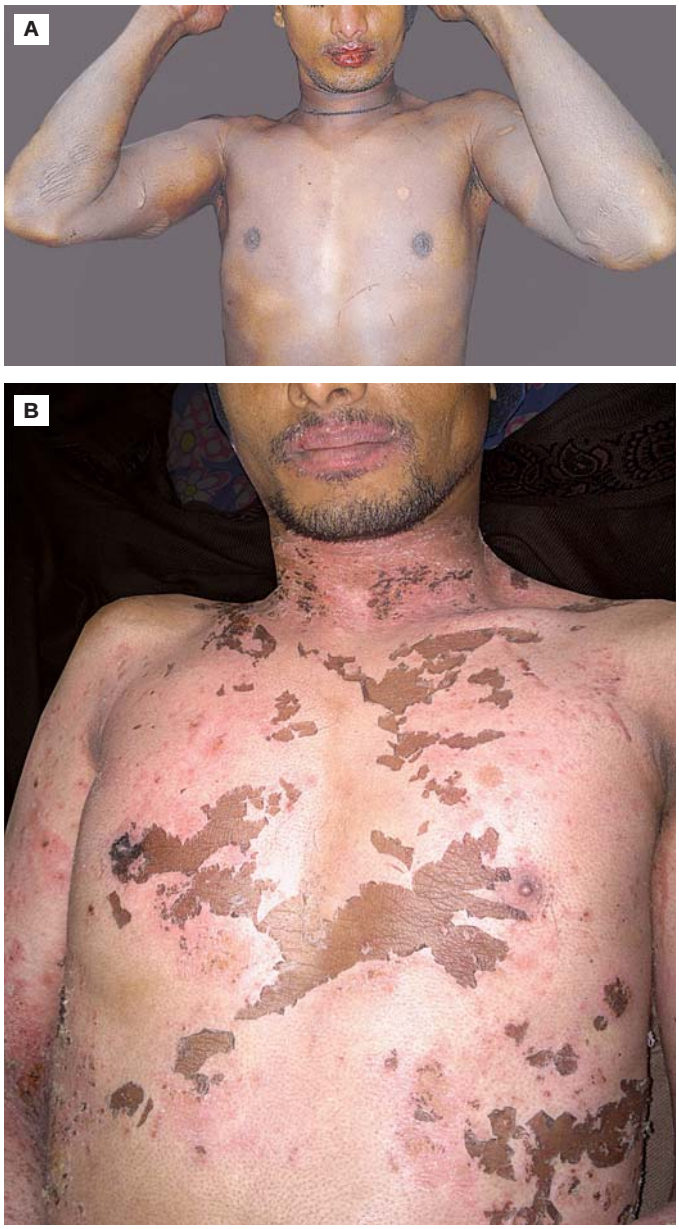

Fig. 13.8: (A & B) Generalized bullous FDE, pre and post-treatment. Paracetamol was suspected as the cause.

resemblance, both clinically and histologically.[23] The confusion between GBFDE and TEN has historically been acknowledged by Lyell also, who admitted that two of the four cases originally described by him as TEN should have actually been diagnosed as GBFDE.[24] The view that GBFDE has a relatively better prognosis than SJS or TEN has recently been challenged. In a comparative study matched for age and extent of skin detachment between GBFDE and SJS or SJS/TEN, it was found that the mortality rate was slightly but not significantly lower for GBFDE and that the reputation of the benign nature of GBFDE should be reconsidered.[24] Despite the close resemblance between the two conditions, they can be differentiated (Table 13.1).

Inverse FDE

Inverse (flexural) FDE is thought to be a variant of the SDRIFE and clinical features of both may overlap. The lesions symmetrically present as well-demarcated, erythematous plaques in the gluteal cleft and other flexures.[25]

Linear/Zosteriform FDE

The lesions occur linearly along the dermatome (Fig. 13.9), possibly as an immune response to previously

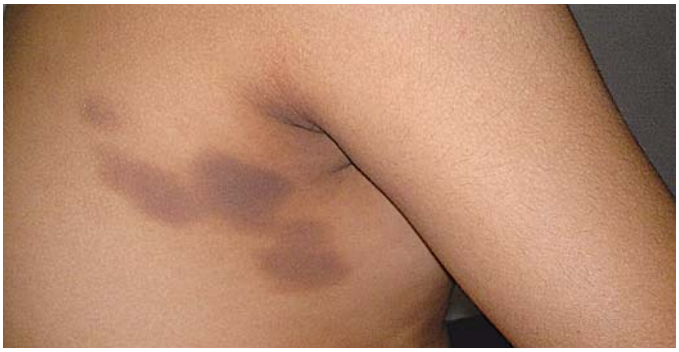

Fig. 13.9: Linear FDE on trunk.

Table 13.1: Differentiating features between GBFDE and TEN

Features	GBFDE	TEN
Morphology of cutaneous lesions	Well-demarcated blisters and erythematous macules with intact intervening skin	Ill-defined, discrete to confluent purpuric macules without intact intervening skin
Mucosal erosions	Absence/paucity	Prominent and severe, two or more mucosae affected
Target lesion	Absent	Atypical target +/–
Constitutional symptoms	Absent/mild	Marked
Systemic involvement	Usually absent	Invariably present
Clinical course and sequelae	Rapid healing and shorter recovery time without sequelae	Delayed healing and longer recovery time, sequelae common
History of recurrence	More likely	Less likely
Histopathology	Abundant infiltration by lymphocytes in skin	Silent dermis

unrecognized/subclinical herpes zoster infection representing an isotopic phenomenon.[26] It has been reported with levofloxacin[27] and trimethoprim.[9] Sometimes, it may be confused with linear lichen planus.[28]

Wandering FDE

The lesions of FDE characteristically recur at the same site upon rechallenge with the offending drug, and thus the name "fixed." However, the involved sites may not necessarily flare with each exposure and the lesions may not always recur at the same sites with each flare in so-called wandering type of FDE. This perhaps occurs because of a prolonged refractory period and the tendency of lesions to become completely refractory in some locations. Wandering FDE has been reported with acetaminophen.[29]

Chronic FDE

Although FDE has acute clinical picture that subsides within a few days, lesions persisting for several months and resembling parapsoriasis en plaque has been described to paracetamol.[30] Characteristic features of classical FDE lesions i.e. resolution upon withdrawal of causative drug and the reproducibility of eruptions by administration of the causative drug are present. This chronic form is due to continued administration of causative drug rather than intermittent use as seen in classic form.[31]

Cellulitis-like FDE

An erythematous and edematous plaque with undermined borders mimicking cellulitis has been reported due to topotecan[32] and paracetamol.[33] Lesions recurred at the same site when drug was readministered.

Psoriasiform FDE

It has been described with nimesulide.[34] The lesions morphologically resemble psoriasis.

Neutrophilic FDE

The classical histopathological finding in FDE consists of an interface dermatitis with predominantly lymphocytic cell infiltrate. In the so-called neutrophilic FDE, a predominantly neutrophilic infiltrate is seen on histopathological examination.

Erythema Dyschromicum Perstans-Like FDE

The erythema dyschromicum perstans (EDP)-like FDE has been reported to theophylline in which the flare occurred both with and without exposure to causative drug. In the immunohistochemical staining, intraepidermal T cells distributed between basal and suprabasal keratinocytes, suggestive of FDE, were seen.[36]

FDE with Pigmentary Loss

In this rare variety of FDE, the initial lesion typically heals with hyperpigmentation and secondarily develops depigmentation in the middle of the lesion. The depigmentation may be postinflammatory or due to destruction of melanocytes.[37]

Postcoital FDE

Cases of FDE to co-trimoxazole have been reported in patients who were not taking any medication, but developed FDE after a few hours following sexual contact with their partners taking co-trimoxazole.[38,39]

Fixed Food Eruption

FDE may be triggered to foods or food additives rather than medications. Such eruptions are referred to as "fixed food eruptions." The term was coined by Kelso in 1996 while describing a fixed eruption triggered by ingestion of strawberry.[40] It has also been described with other foods such as peanut,[41] cashew,[42] lentil,[43] lactose,[44,45] and tartrazine-containing foods.[46]

The food-specific IgE has been demonstrated by immunoblotting technique and the lesions have been suggested to result from immediate hypersensitivity rather than delayed hypersensitivity as seen in FDE.[41]

PATHOGENESIS

FDE is a type of classical delayed hypersensitivity reaction in which resident T cells of effector/memory phenotype are proposed to be the key mediators in "eliciting" the FDE lesions. Upon resolution of FDE lesions, these $CD8^+$ T cells remain lodged at the dermoepidermal junction in a quiescent state till drug rechallenge. These cells get reactivated and expand on subsequent re-exposure to the offending drug with the release of interferon (IFN) and other cytokines leading to apoptosis of keratinocytes. Later, regulatory T cells accumulate at the site and limit further immune damage by inhibiting the activity of the cytotoxic T cells. Expanded and activated cytotoxic T cells get removed to a large extent by apoptosis. However, a small population of these cells is prevented from apoptosis by keratinocyte-derived interleukin-15 and remain as skin-resident T cells until the next activation cycle (Fig. 13.10).[17]

DRUGS CAUSING FDE

A wide variety of drugs have been implicated to cause FDE (Table 13.2). The list is ever growing on

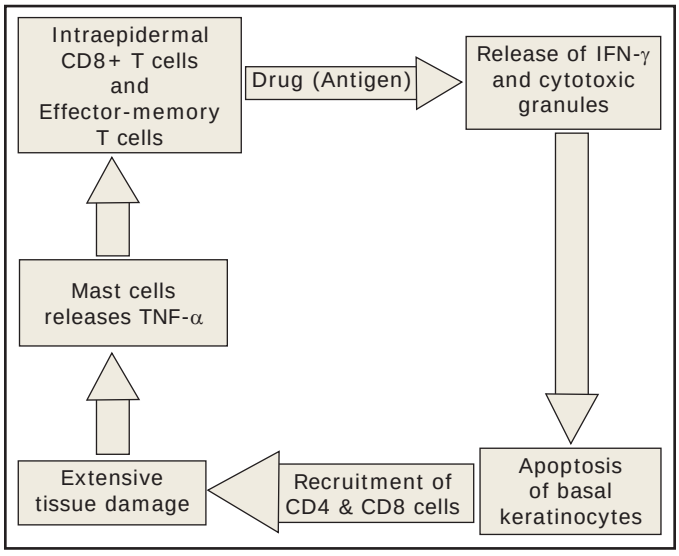

Fig. 13.10: Pathogenetic mechanism in FDE.

account of introduction of newer drugs and enhanced pharmacovigilance. The pattern of drugs causing FDE differs from place to place depending on the prescribing trend and availability of drugs in that particular region.[47] Phenolphthalein, once a common offender,[48,49] has been replaced by other agents like quinolones and imidazole derivatives. The drugs reported to cause FDE are listed in Table 13.2.

CROSS-SENSITIVITY AND POLYSENSITIVITY

Sometimes, multiple drugs with similar chemical structure may cross-react and induce FDE in the same individual. This is referred to as cross-sensitivity. In polysensitivity or polyallergic sensitization, the patient is sensitive to various drugs with totally different chemical structures. In such cases, the lesions of FDE may occur at different sites with different drugs. These chemically unrelated drugs might have been used for the same or different disorders.[50–52] It has been suggested that polysensitivity is much more common than is actually reported and may have been overlooked in the past because of relatively low recognition of this phenomenon.[31]

Sometimes, FDE is caused by combination of drugs, but not by either of the drugs given separately. Such instances highlight the situation in which polypharmacy may result in drug interactions, leading to the formation of chemicals toxic to the body.[53]

HISTOPATHOLOGY

The histopathological features depend on the stage of the lesion biopsied. The early lesions of FDE exhibit an interface reaction pattern with vacuolar degeneration of basal keratinocytes, dermal edema,

Table 13.2: Drugs causing FDE

Group	Drugs
Antibacterials	Tetracyclines* Penicillin: Ampicillin, amoxicillin* Sulfa drugs: Sulfamethoxazole, trimethoprim* Erythromycin Rifampicin Clarithromycin Fluoroquinolones© Metronidazole, tinidazole, ornidazole*
Antifungals	Griseofulvin Fluconazole Ketoconazole Terbinafine
Antipsychotics	Barbiturates Anticonvulsants Opium alkaloids Chlordiazepoxide Chloral hydrate Oxazepam Carbamazepine
NSAIDs	Phenylbutazone, oxyphenbutazone Aspirin Ibuprofen* Acetaminophen* Diclofenac Naproxen Piroxicam* Mefenamic acid Etoricoxib and celecoxib
Antihistamines	Hydroxyzine hydrochloride Cetirizine hydrochloride Loratadine Diphenhydramine
Decongestants	Amlexanox Citiolone Pseudoephedrine* Codeine
Miscellaneous	Allopurinol Acyclovir, valacyclovir, famciclovir Atenolol Albendazole Carbocisteine* Chlorhexidine Clioquinol Colchicine Cyclizine Cyproterone acetate Dextromethorphan Dipyrone Dimenhydrinate Docetaxel Ethenzamide Finasteride Foscarnet Furosemide IFN β-1b Phenolphthalein Tenoxicam Ticlopidine Botulinum toxin Papaverine Paclitaxel Lormetazepam Procarbazine

* Commonly incriminated drugs

and a perivascular lymphocytic infiltrate in upper dermis. Healed or resolved lesions are characterized by melanophages in the upper dermis. The NPFDE lacks this characteristic feature. If the keratinocyte damage is extensive as in GBFDE, biopsy changes can be mistaken for transepidermal necrosis of TEN.

DIAGNOSIS

The diagnosis of FDE is primarily based on characteristic clinical picture and is easy even when the active disease has subsided on account of the characteristic residual hyperpigmentation. The recurrence of the lesions at the same site upon readministration of culprit drug is a useful pointer to the diagnosis (Fig. 13.10). A meticulous history of drug intake both prescriptional and over the counter, regular or intermittent including oral, intravenous, sublingual, per-rectal, inhalants, and intradermal should be sought. Food additives, preservatives, and coloring agents should also be thought of as a rare cause of FDE. The confirmation of the culprit agent may be substantiated through oral or topical provocation.[54,55]

Oral Provocation Test

It is a gold standard method to ascertain the incriminating drug and involves reproduction of the reaction using a subtherapeutic dose under supervised condition. It is particularly helpful in patients consuming multiple drugs whose nature is unknown. It is also helpful in generating a list of safe alternative drugs for the future use. After an adequate washout period of 4 weeks and obtaining the written consent, the procedure is carried out, starting with a placebo and followed by administration of graded/incremental dose of suspected medications. The least suspected drug should be tested first, followed by other drugs in the order of suspicion. The patient should not be on antihistamines, topical or systemic corticosteroids, or other immunosuppressive drugs at least for 4 weeks before and during provocation.[3]

Topical Provocation/Patch Testing

Topical provocation is relatively safe compared to the oral that may at times lead to generalized bullous lesions.[56] It is particularly useful in children and in cases of GBFDE. When a drug is strongly suspected to be the cause of reaction, a safer approach may be performing patch testing as the initial diagnostic tool followed by oral provocation test when the topical patch tests are negative even with the incremental concentration of the topical agent. However, the concentration of the drug to be used for individual patient is still not standardized. It is generally undertaken with pure original drug, diluted in 1%–10% of white petrolatum at the previously involved sites. A positive test at the previously involved site is a strong evidence that the FDE lesions are caused by the tested drug. However, a negative test does not necessarily rule this out.

Intracutaneous Scratch Test

The diagnostic value of this test is equivocal with studies both supporting[57] and refuting[14] its reliability.

DIFFERENTIAL DIAGNOSIS

The diagnosis of FDE is usually considered to be straightforward. However, with recognition of unusual forms, the clinical spectrum of the disease is ever expanding. The clinical and histopathological differential diagnoses of FDE are discussed in Tables 13.3 and 13.4, respectively.

TREATMENT

The essential step in the treatment of FDE is the identification and elimination of the incriminating drug(s) and avoidance of the offending drugs or chemically related drugs. This is, however, not always easy if the nature of the drugs consumed is not known. In the active stage, symptomatic relief of pruritus may be achieved with oral antihistamines and/or topical corticosteroids. The inflammatory lesions spontaneously resolve within 2–3 weeks of discontinuation of the offending drug. Hyperpigmentation may spontaneously resolve over a period of a few months to years unless patient is re-exposed to the offending agent. Secondarily infected erosions may be treated with topical or systemic antibiotics. Moist compresses using saline or diluted potassium permanganate solution followed by frequent application of petrolatum base ointment may be helpful to prevent and loosen the crusts on the lip mucosa. Painful oral lesions may be treated with solutions containing viscous lidocaine and topical steroids. Systemic steroids may be used to treat the extensive lesions of GBFDE.

Table 13.3: Clinical differential diagnosis of FDE

Morphology	Conditions	Differentiating features
A. Localized erythematous macules and plaques	Urticaria	Evanescent, itchy, edematous plaques, vesicle and bulla absent. No residual pigmentation
	Urticarial vasculitis	Relatively shorter course of individual lesions, less intense pigmentary changes, associated systemic symptoms more frequent
	Polymorphous light eruption	Lesions over sun-exposed area, polymorphous
	Cellulitis	Edema and tenderness, systemic symptoms usual
B. Vesicle and bullae	Erythema multiforme	Target lesions, acral and symmetrical distribution, usually infection related
	SJS/TEN	More widespread lesions, atypical target and purpuric lesions, sheet-like peeling of skin, severe mucosal involvement (>2), severe constitutional symptoms
	Pemphigus vulgaris	Flaccid bulla, more widespread, protracted course, positive Nikolsky sign
	Bullous pemphigoid	Elderly patient, tense symmetrical bullae, intense itching, prolonged course
C. Oral–genital mucosal	Oral lichen planus	Usually more persistent, protracted course
	Aphthous ulcers	Intensely painful, necrotic and smaller lesions
	Fuchs' syndrome	*Mycoplasma pneumoniae* associated, oral and genital mucosal involvement, hemorrhagic crusting, constitutional symptoms usual
D. Quiescent/residual pigmentary stage	Postinflammatory pigmentation	History of preceding dermatoses such as lichen planus, psoriasis, pityriasis rosea, immunobullous disease
	Urticaria pigmentosa	Usually in children, more symmetrical and uniform-sized lesions, Darier's sign+
	Erythema dyschromicum perstans	Asymptomatic, slow evolution of lesions, active border usual

Table 13.4: Histopathological differential diagnosis of FDE

Condition	Histopathological differentiating features
Erythema multiforme	Infiltration usually superficial and relatively less number of melanophages
SJS/TEN	Necrotic keratinocytes that may progress to confluent epidermal necrosis, silent dermis
Acute graft versus host disease	Satellite cell necrosis
Lupus erythematosus	More interface changes with intense lymphocytic infiltrate, basement membrane thickening, dermal mucin deposition, perivascular, and "periadnexal" lymphoid aggregate
Lichen planus	Wedge-shaped hypergranulosis, sawtooth rete ridges, band-like lymphohistiocytic infiltration
Pityriasis lichenoides chronica (PLC)/ Pityriasis lichenoides varioliformis et acuta (PLEVA)	Relatively less vacuolar interface change, dyskeratotic keratinocytes, red blood cell (RBC) extravasation in dermis, infiltrate predominantly lymphocytic

LEARNING ESSENTIALS

- FDE is a common reaction pattern characterized by the fixed localization of lesions on repeated administration of the same drug.
- The lesions heal with characteristic hyperpigmentation, a feature that helps in the diagnosis even in quiescent stage.
- The unusual and uncommon presentation of FDE is increasingly recognized and clinicians should be aware of these in order to miss the diagnosis.
- The list of common drugs causing FDEs constantly keeps changing because of introduction of newer drugs, their availability, and prescription trends.
- Oral provocation test is the gold standard method to ascertain the causative drug.

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Chapter

14

Exanthematous Drug Reactions

Imran Majid • Shagufta Rather

SUMMARY

- Exanthematous drug reactions (EDRs), also called morbilliform or maculopapular drug rash, are one of the most common cutaneous adverse drug reaction patterns.
- Lesions are usually polymorphous with erythema, macules, and papules; initially discrete, and may later get confluent. A variable degree of pruritus is generally present.
- Incidence and specific drugs responsible for EDR differ between population groups.
- Patients with certain viral infections such as Epstein–Barr virus and HIV infection and who have undergone bone marrow transplantation are at increased risk.
- Antibiotics, antiepileptics, allopurinol, non-steroidal anti-inflammatory drugs (NSAIDs), and antiretroviral drugs are some of the common offending drugs.
- Identification and elimination of the causative drug is the most important step in the management; symptomatic treatment with antipruritic agents and potent topical glucocorticoids may be helpful.
- A benign exanthematous rash may sometimes be a sign of more sinister multisystem reactions such as Stevens–Johnson syndrome, toxic epidermal necrolysis, erythroderma, or drug hypersensitivity syndrome.
- Some of the "red flag signs" that should alert the clinician to the possibility of these severe reactions include high fever, facial edema, skin tenderness, mucous membrane involvement, bullae and lymphadenopathy.

INTRODUCTION

Exanthematous drug reactions (EDRs) are the most frequently encountered adverse drug reactions (ADRs) involving the skin. They are also sometimes called as morbilliform or maculopapular drug eruptions. The eruption typically develops a few days to some weeks, following the drug administration. Benign EDRs are typically uncomplicated by severe systemic symptoms or internal organ involvement. The lesions are polymorphous with primary efflorescence such as macules, papules, or a combination of both and usually accompanied by pruritus of variable degree. Rarely, vesicles, pustules and bullae, and secondary lesions such as scales, erosions, and hemorrhage may be observed.[1] Several drugs (Table 14.1) have been reported to cause EDR.[2–5] Incidence and specific drugs responsible for EDR differ between population groups (Table 14.2).

Table 14.1: Drugs commonly implicated in EDRs

Class of drug	Drugs
Antibacterials	Penicillins, cephalosporins, sulfonamides, fluoroquinolones, tetracyclines
Antivirals	Abacavir, nevirapine, efavirenz, amprenavir, tenofovir, ritonavir, fosamprenavir
NSAIDs	Diclofenac, ibuprofen, aspirin, oxicam
Antiepileptics	Carbamazepine, lamotrigine, phenobarbital, phenytoin
Antimalarials	Chloroquine, hydroxychloroquine
Tricyclic antidepressants, SSRIs	Lithium carbonate, paroxetine, fluoxetine, sertraline
Antipsychotics	Chlorprothixene, clozapine, haloperidol, olanzapine, risperidone, ziprasidone
Others	Allopurinol, terbinafine

SSRI - selective serotonin reuptake inhibitor;
NSAID - nonsteroidal anti-inflammatory drug.

Table 14.2: Studies on relative incidence of exanthematous drug reaction and the causative drugs

Study	Study population	Study design	CADR pattern (%)	Drugs implicated (%)
Choon et al.[2]	362 patients M/F: 1.14:1 Age: 20–59 years Mean age: 39.6	10-year, data analysis by CADR registry	EDR: 42.3 SJS: 24.3 DRESS: 9.4	• Antibiotics (44.3): penicillins, sulfonamides, dapsone • AED (22.4): phenytoin, carbamazepine, lamotrigine • Antigout (13.8): allopurinol
Tian et al.[3]	22,866 inpatients F: 69%	Prospective, hospital-based study	EDR: 40 Urticaria: 23.1	• Antibiotics (36.9%) • ICM (18.5%) • NSAID (18.5%)
Patil et al.[4]	3671 patients Age: 1–80 years M: 52.49%	18–year, meta-analysis/ systematic review of CADR in Indian population	EDR: 32.39 FDE: 20.13 Urticaria: 17.49	• Antibiotics (45.46%): sulfa, β-lactams, fluoroquinolones, nitroimidazole • NSAIDs (20.87%): ibuprofen, diclofenac and aspirin • AED (14.57%): carbamazepine (6.65%), phenytoin (6.46%)
Salazar et al.[5]	4785 patients	10-month, prospective cohort study	EDR: 51.2 Urticaria: 12.2 Erythema multiforme: 4.9	• Antibiotics(48.8%): amoxicillin/ clavulanate, amphotericin B, metronidazole • NSAID (18.6%)
Puavilai et al.[6]	212 patients M/F: 1:1.7 Mean age: 46 years	1-year, hospital-based, multicentric, cross-sectional study	EDR: 55.4 FDE: 21.4 Urticaria: 8.3	• Antimicrobials (50.0): penicillins, sulphas, fluoroquinolones • NSAIDs (14.8): ibuprofen, diclofenac, aspirin • Drugs acting on CNS (10.6)
Rahmati et al.[7]	54 patients M/F: 1.3:1	6-year, hospital-based study	EDR: 60 Erythroderma: 10 Urticaria: 10	• AED (31): phenytoin, carbamazepine, phenobarbital, lamotrigine • Antibiotics (28): amoxicillin, trimethoprim/ sulfamethoxazole, penicillin, ciprofloxacin, vancomycin
Garg et al.[8]	43 patients M: 46.5% Age: 30.07 ± 13.63 years	2–year, hospital-based cross-sectional study	EDR: 48.8 Erythroderma: 18.6 Urticaria: 11.7 FDE: 11.7	• Antibiotics (48.8): amoxicillin, ciprofloxacin, cefotaxime, cefuroxime, co-trimoxazole, clarithromycin • NSAIDs (32.5): ibuprofen, piroxicam, celecoxib, diclofenac
Sushma et al.[9]	3541 patients M: 52%	9–year, retrospective study	EDR: 42.7 SJS: 19.5 FDE: 11.4	• Antibiotics (45): cephalosporin, fluoroquinolones • AED (19): phenytoin, carbamazepine • NSAIDs (19): diclofenac, ibuprofen
Sharma et al.[10]	500 patients M: 59.6% Mean age: 34.5 years	6–year, hospital-based prospective study	EDR: 34.6 FDE: 30 Urticaria: 14	• Antibiotics (42.6%): sulfonamides, penicillins,macrolides, fluoroquinolones • Antitubercular drugs • AED (22.2%): Phenytoin, carbamazepine, phenobarbitone • NSAIDs (18%): Salicylates, ibuprofen
Bharani et al.[11]	231 patients Age: 2–40 years	1-year, cross-sectional, observational study	EDR: 41.12 Steroid damage: 18.18 Urticaria: 8.6	• Antibiotics (35%): cephalosporins, fluoroquinolones, metronidazole • NSAIDs (17.32%): paracetamol, diclofenac, ibuprofen • AED (7.79%): phenytoin, phenobarbitone
Turk et al.[12]	2801 patients F: 59.6%	5-year, hospital-based retrospective study	EDR: 59.6 Erythroderma: 6.4 DRESS: 6.4	• Antibiotics (24.5%) • NSAIDs (22.4%) • AED (13.8%)
Mokhtari et al.[13]	282 patients F: 60.8% Mean age: 29.48 ± 21.18 years	8-year, retrospective hospital-based study	SJS: 31.9 EDR: 24.5 TEN: 11	• AED (51.8%): lamotrigine, carbamazepine, phenobarbital, phenytoin • Antibiotics (33.7%): penicillin, co-trimoxazole, cefixime, amoxicillin • NSAID (5.7%): ibuprofen

AED - antiepileptic drug; CADR - cutaneous adverse drug reactions; CNS - central nervous system; DRESS - drug reaction with eosinophilia and systemic symptoms; EDR - exanthematous drug reaction; FDE - fixed drug eruption; ICM - iodinated contrast media; NSAID - nonsteroidal anti-inflammatory drug.

FACTORS THAT AFFECT THE RISK OF DEVELOPING EXANTHEMATOUS DRUG REACTIONS

Many patient-related factors affect the risk of developing EDR to a particular drug. These include the following:[14]

1. Alterations in immune status: Patients with immunosuppression especially those affected by HIV are at an increased risk for developing cutaneous adverse drug reaction (CADR) including EDR. Similar is the case with bone marrow transplant recipients.
2. Infections: Certain viral and other infections also increase the risk of EDR with either a particular drug or with many drugs. A typical example is infectious mononucleosis that greatly increases the chances of EDR with aminopenicillins.
3. Genetic factors: Certain human leukocyte antigen (HLA) are associated with an increased risk of EDR. These include HLA-A*3101 that increases the risk of carbamazepine-induced drug rash manifold.
4. Other factors: These include female sex, old age, polypharmacy, history of CADR, and concomitant autoimmune diseases.

PATHOGENESIS OF EDR

Pathogenesis of EDR mainly involves a delayed, type IV hypersensitivity reaction.[15]

The pathogenic events in the development of an EDR are shown in Fig. 14.1.

Upregulation of cytokines and chemokines has been reported as a result of drug-induced EDR. Increase in interferon gamma (IFN-γ) accounts for the upregulation of major histocompatibility complex (MHC) class-II on keratinocytes, which allows drug presentation to $CD4^+$ T cells. Interleukin (IL)-5 and eotaxin (CCL-11), upregulated in EDR explains the increased number of eosinophils typically seen on histology in such cases. Additionally, recruitment of $CD4^+$ and $CD8^+$ T cells in EDR can be partly attributed to CCL-27–CCR10.[16]

New concepts in the etiopathogenesis of these drug reactions including direct binding of drugs lacking hapten characteristics to T cell receptors (pi concept) and direct activation of HLAs bypassing the processing by antigen presenting cells have come into focus.[17]

CLINICAL PRESENTATION

The eruption typically starts as bright erythematous

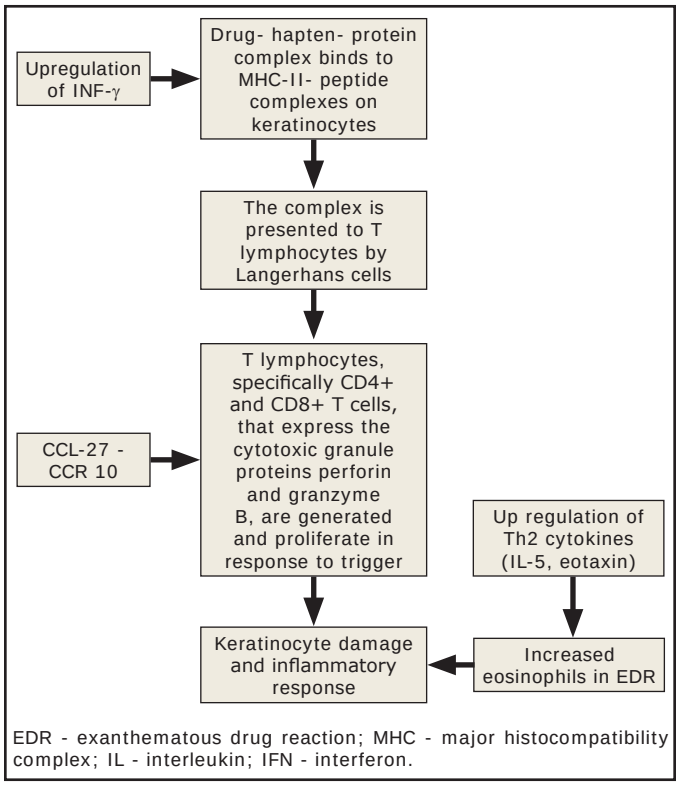

Fig. 14.1: Pathogenesis of EDRs.

macules, initially on the trunk which progressively become confluent and spread peripherally in a symmetric fashion (Fig. 14.2). The eruption may generalize (Fig. 14.3) and involve the entire body including palms and soles. The extremities and intertriginous areas are often involved. The eruption is commonly accompanied by pruritus and low-grade fever.

These lesions usually appear within 1 week or at any time upto 3 weeks of initiating the offending medication and resolve spontaneously within 7–14 days, with a change in color from bright red to brownish red, which may be followed by scaling or desquamation. However, the eruption may develop much earlier in case of inadvertent rechallenge.[1]

Rash is typically polymorphous, with morbilliform, scarlatiniform, or sometimes urticarial or atypical targetoid lesions reminiscent of erythema multiforme.[1] Sometimes purpuric tinge may be seen, aggravated by scratching (Fig. 14.4). Erythroderma (Fig. 14.5) may result due to confluence of lesions and may portend relatively severe nature of reaction. Mucous membranes are usually spared.

Danger Signs: Clinicians should be mindful of the fact that at times severe forms of drug reactions such as drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens–Johnson syndrome (SJS), or toxic epidermal necrolysis (TEN) may initially

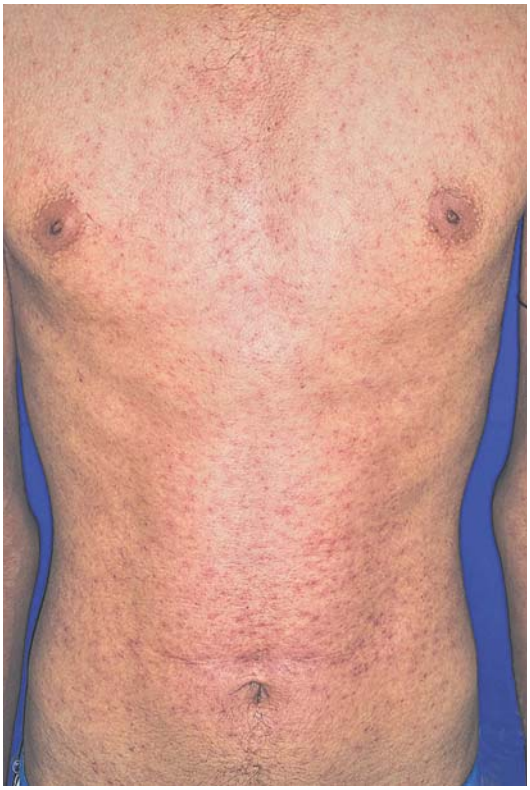

Fig. 14.2: Discrete maculopapular rash over trunk.

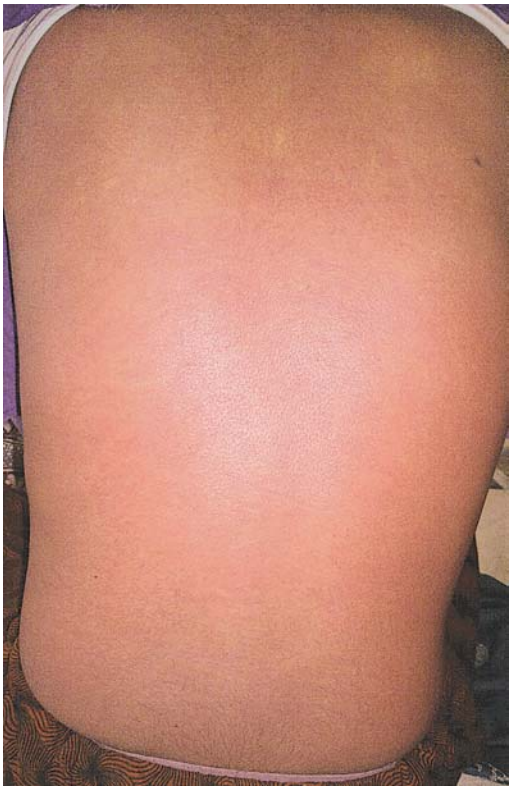

Fig. 14.3: Lesions coalescing to form generalized exanthematous rash over back, caused by ampicillin intake.

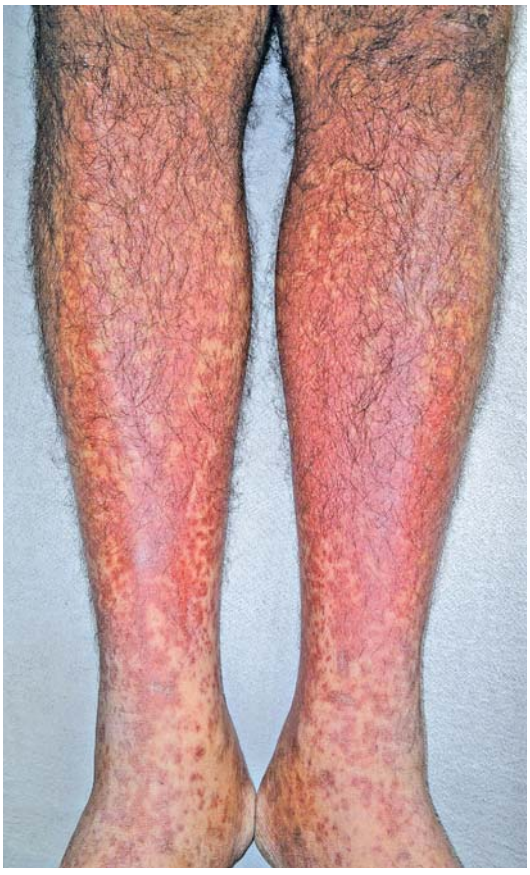

Fig. 14.4: Purpuric tinge in lesions of EDR.

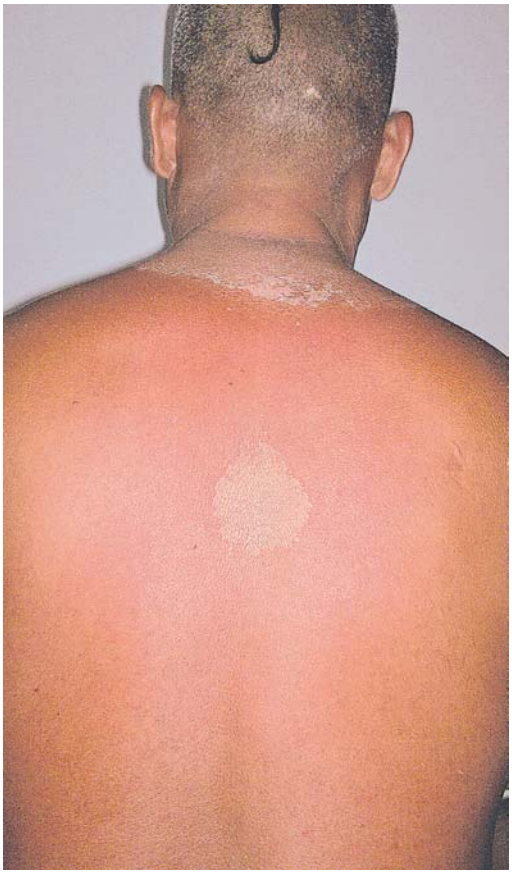

Fig. 14.5: Impending erythroderma in a patient with maculopapular drug rash.

present as maculopapular drug reactions before evolving into these more sinister diseases. The **"red flag signs"** that herald a more serious disease include the presence of widespread exanthema, induration, necrosis, bullae (Fig. 14.6), pustules, purpura, ulcers, mucosal involvement, facial edema (Fig. 14.7), and pain in skin. Nikolsky sign, fever, and signs of systemic involvement should also alert the clinician to the possibility of a severe reaction.

HISTOPATHOLOGY

Histopathology of EDR tends to be nonspecific; the changes are generally those of spongiotic dermatitis (97%) with a greater involvement of the lower layers, often accompanied by mild hyperplasia (72%), in conjunction with interface dermatitis of the vacuolar type. Mild lymphocyte exocytosis and occasional necrotic keratinocytes in suprabasal layers are seen.[15,16]

Frequently observed pattern is a superficial and deep perivascular mixed infiltrate in the dermis, composed of lymphocytes (100%) and eosinophils (60%) accompanied by neutrophils (50%). The reticular dermis may have an interstitial infiltrate composed of more eosinophils than neutrophils.[15,16]

The histologic differential diagnosis of morbilliform drug eruption includes viral exanthemata, fixed drug eruption, erythema multiforme, acute graft-versus-host disease (GVHD) and acute lupus erythematosus. Viral exanthemata are difficult to differentiate from morbilliform drug eruption. The presence of eosinophils in the cutaneous ADRs is more frequent and marked in EDR than in viral exanthemas, but is not specific.[18]

The presence of satellite cell necrosis tracking down the follicle in acute GVHD helps to distinguish it from morbilliform drug eruptions. Additionally, neutrophils and eosinophils are rare in GVHD.[18]

DIFFERENTIAL DIAGNOSIS

EDRs are the most common cutaneous adverse drug reactions, but their frequency could be overestimated because the differential clinical diagnosis from viral and bacterial exanthems is not always easy.[18] The polymorphic nature of the cutaneous eruption and the presence of peripheral blood eosinophilia favor a drug reaction.

The major entity in the differential diagnosis of EDR is a viral exanthema. Others include toxic shock syndromes, scarlet fever, acute GVHD, Kawasaki disease and Still's disease. Table 14.3 shows some helpful differentiating clinical features.

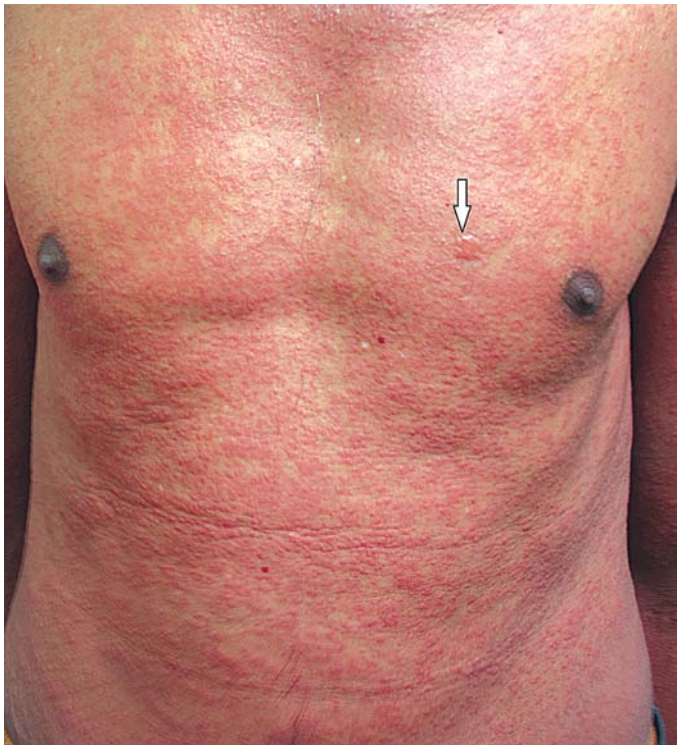

Fig. 14.6: Appearance of bulla (arrow) in EDR should be considered a "red flag" sign.

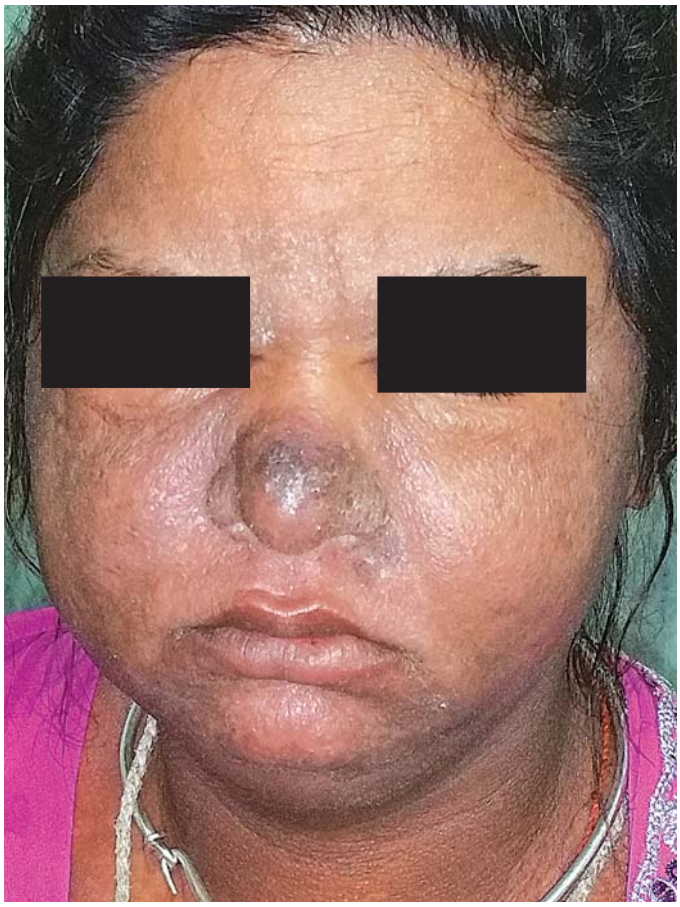

Fig. 14.7: Facial edema, in EDR is a warning sign for impending DRESS. Erythema and scaling in a patient with EDR.

Table 14.3: Characteristics that help to differentiate various infectious and other exanthems from an exanthematous drug reaction

Diagnosis	Age	IP	Prodrome	Description and distinguishing features
Measles (rubeola)	Infant to young adult	8–12 days	Fever, cough, coryza, conjunctivitis; for 3–4 days	Erythematous maculopapular rash, confluent, on day 4, usually itchy, often extends rapidly from face and neck to the trunk and limbs. Koplik's spots (pathognomonic) helps to establish the diagnosis. Furfuraceous desquamation occurs after 6–7 days.
Rubella (German measles)	Adolescent to young adult	16–18 days	Low-grade fever, malaise, coryza, conjunctivitis for 1–5 days	Maculopapular rash, nonconfluent, extends from face to trunk to limbs, milder than those seen in measles, usually resolves within 3 or 4 days. The rash is often accompanied by fever, retroauricular and suboccipital adenopathy, and arthralgias. Forchheimer's spots (palatal petechiae) are present.
Roseola infantum (exanthema-subitum)	<3 years	5–15 days	High-grade fever for 3–5 days	Rash starts with a defervescence, as a pink, short-lived, nonconfluent maculopapular eruption. The rash usually starts on the trunk and spreads to the face and extremities and fades in hours to 2 days. Adults have cervical adenopathy, with variable rash and fever that may last for months.
Erythema infectiosum (fifth disease)	>5–15 years	6–14 days	Minimal prodrome	Fever with characteristic "slapped cheeks" develops 2–4 days before generalized maculopapular rash, which begins on proximal extremities and spreads to trunk and peripherally. The rash often has a livedo/reticular pattern secondary to central fading, resolves in a month.
Infectious mononucleo-sis	15–25 years	30–50 days	Headache and fatigue for 3–5 days	Begins with fever, pharyngitis, hepatosplenomegaly, supraorbital edema. A maculopapular rash, mainly on trunk, seen in 10%–15%, on fourth to sixth day. In adolescents and adults, rash is usually associated with aminopenicillin administration, with an onset within 3 days after administration (a more rapid onset than is usual for drug eruptions).
Acute graft-versus-host disease				The rash typically occurs 2–4 weeks after transplantation. It may be pruritic. If generalized, the rash is often difficult to distinguish clinically from an exanthematous drug eruption.
Acute HIV seroconver-sion				An acute onset of exanthematous rash, 1–6 weeks after infection in a symmetric distribution involving the face, palms, and soles. Oral and genital aphthous-type ulcers may occur. It is usually accompanied by fever, malaise, myalgias, arthralgias, and lymphadenopathy.
Scarlet fever	School-aged children	3–5 days	High fever, pharyngitis, vomiting, pain abdomen for 2–4 days	Rash begins within 24 hours of symptoms. Punctiform, erythematous papular (sandpaper) confluent red rash that blanches and desquamates on fourth day. Cervical lymphadenopathy, strawberry tongue, pastia's lines (petechiae in intertriginous areas) are characteristics.

IP - incubation period

DIAGNOSIS AND APPROACH TO A PATIENT WITH EDRS

The diagnosis and ascertainment of the culprit drug and differentiation from the other mimickers is usually accomplished mainly on the clinical grounds. A few investigative tools may, however, be useful but no single laboratory test can replace a good characterization of these clinical parameters. The approach to EDR comprises of a thorough clinical and diagnostic workup. The goal is to evaluate whether the rash is drug induced and if yes, which is the most likely drug responsible. This is easy if the patient has taken only a single drug but very difficult in situation where the patient has consumed multiple drugs, which is often the case. A decision whether

to discontinue the drug (if the reaction is severe) or to adopt a "treat through" approach (if it is a milder rash and is likely to abate despite the continued use of drug) is very important. The evaluation should also be aimed at recognizing the warning sign of a more sinister and potentially life-threatening reaction like drug hypersensitivity syndrome (DHS) or SJS/TEN, which could initially present as maculopapular rash. Finally, a thorough counselling about the avoidance of suspected and structurally related drug(s) and use of the safer substitutes instead should be done. A few of the following laboratory investigative tools may be used but none of them is specific to EDR:

1. *Skin biopsy*: The presence of mixed pattern in a specimen, eosinophils, edema, inflammation, and apoptotic keratinocytes is a clue for the diagnosis of a drug eruption.[19] Skin biopsy may not be helpful for identifying a drug eruption or in discriminating between drug-induced exanthems (DIEs) and viral–bacterial exanthems, as the histopathological changes are often nonspecific.
2. *Patch test*: The participation of drug-specific T cells in these drug eruptions makes patch testing helpful in EDR.[20,21] Patch tests with drugs can be particularly helpful in determining the culprit drug in various types of drug eruptions and to study relevant cross-reactions between drugs. It is easy to perform and is relatively safe.
3. *Intradermal and skin prick tests*: These tests with late readings can be helpful when patch tests are negative, with variable efficacy.[22]
4. *In vitro tests*: These tests such as lymphocyte transformation tests (LTTs) or lymphocyte stimulation tests (LSTs), IFN, and IL-4 ELISpot help in faster identification of incriminating drug and thus can be useful adjunct tools in the diagnosis of these drug eruptions. Nevertheless, these procedures are not standardized, results are inconsistent with undetermined sensitivity and specificity, and therefore, they are not performed on a routine basis.[19]
5. *Drug provocation test*: The most sensitive and specific diagnostic test for drug eruptions is the drug provocation or rechallenge test. The primary aim is to exclude drug hypersensitivity, but can be used to confirm diagnosis and also helpful in generating a list of safe drug(s) for future use.[23]

COURSE AND PROGNOSIS

Once the causative drug is identified and suspended, the reaction generally subsides within 1–2 weeks after discontinuation of the offending agent. In case of drugs with longer half-lives such as anticonvulsants, the rash may take longer time to subside. EDR may occasionally evolve into erythroderma when it takes longer time to subside. The overall prognosis of the patient is good unless the patient develops more serious reactions such as DHS or SJS/TEN.

TREATMENT OF EDR

Treatment of benign EDR is primarily symptomatic and supportive. Initial step is to stop administration of the suspected causative drug. Oral antihistamines and potent topical corticosteroids may be given to alleviate pruritus. If no improvement is seen, an alternative diagnosis should be considered. In severe cases, systemic corticosteroids can be given in injectable or oral form.

LEARNING ESSENTIALS

- EDRs are the commonest drug reaction pattern.
- Differentiation from infective exanthems is not always easy.
- Upregulation of distinct cytokine profile in the skin as a result of DIEs and infective exanthems on immunohistochemistry has recently been found to be helpful in understanding the etiopathogenesis.
- A possibility of severe CADR should be considered if EDR is associated with fever, lymphadenopathy, edema of face, skin tenderness, and necrosis.
- Identification of certain HLA haplotypes and genetic factors that can predict risk of EDR to certain drugs in some "at-risk individuals" is envisaged in future.

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Chapter

15

Lichenoid Drug Reactions

Rajesh Kumar • Vaishali Masatkar • Lalit Kumar Gupta

SUMMARY

A wide variety of drugs and chemicals can induce lichen planus (LP)–like reactions that may be difficult to differentiate from idiopathic LP, both clinically and histologically. Lichenoid drug reactions tend to be more extensive and symmetric without any flexural predilection. Morphology of the lesions may resemble that of typical LP or may be psoriasiform, pityriasiform, or eczematous. The involvement of mucosae and nails is relatively infrequent. The time interval between the initiation of the offending drug and the appearance of the cutaneous lesions as well as time for resolution of lesions after cessation of offending drug is relatively long compared to other drug reactions and varies from months to years. A wide variety of drugs, including biological agents, can cause lichenoid drug reactions (LDRs). Some of the common offenders include gold, antimalarials, methyldopa, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, and penicillamine. Histopathology shows a lichenoid interface dermatitis as in idiopathic LP. The infiltrate tends to be less dense, deeper and pleomorphic with eosinophils and plasma cells in varying proportion. Focal parakeratosis and necrotic keratinocytes in epidermis are additional histological features.

INTRODUCTION

Lichenoid drug reaction (LDR) or drug-induced lichen planus (LP) is fairly common entity encountered in clinical practice. There is no sex predilection, but lichenoid drug reaction tends to affect adults, approximately 10 years older compared to idiopathic LP.[1] Clinically, the lesions tend to be more generalized and may resemble idiopathic LP or may have psoriasiform, pityriasiform, or eczematous appearance.[2]

The latent period may range from months to years, with an average of 2–4 months depending on the nature of drugs, dosage, and duration of therapy.[3] In a study by Halevy et al.[4] on lichenoid eruption induced by drugs, the mean latent period was 12 months. The latent period for penicillamine and β-blockers has been reported to be around 2 months–3 years and 1 year, respectively, and 4–6 weeks for quinacrine.[1] The resolution of lichenoid rash after discontinuation of the offending drug(s) varies from several weeks to months and has been reported to be even 2 years in case of gold salt.[4] This fact is important in management while assessing the drug causality and response to drug withdrawal.

A large number of drugs (Table 15.1) have been reported to cause LDR, and the list is ever expanding. Common group of drugs include antimalarials, antihypertensives, diuretics, and gold salts. Even biological agents such as imatinib[5–7] and etanercept[8,9] have paradoxically been reported to cause LDR. A rash simulating LP has been reported to occur with some vaccines such as influenza and hepatitis B.[10] Several chemicals such as those used in processing of color films (Fig. 15.1), methacrylic acid esters, musk ambrette, dental restorative materials and metals like nickel, silver, and gold (Fig. 15.2) may induce lichenoid reactions.[11] Lesions resembling oral LP, affecting areas adjacent to contact with dental amalgam material and resolving after removal of dental amalgam, have been reported. Patch test positivity to metals such as nickel, mercury, and gold has been demonstrated in these patients.[12]

PATHOGENESIS

The exact pathogenesis of LDR is not known. It is believed to develop as a result of autoreactive T cells directed against a drug–major histocompatibility complex (MHC) antigen complex so that the immune system views keratinocytes and Langerhans cells as "non-self". Cytotoxic $CD8^+$ T cells may play an important role in induction of keratinocyte apoptosis

Table 15.1: Drugs implicated in LDR

Antihypertensive agents	β-blockers: **propranolol**, **labetalol** Angiotensin-converting enzyme (ACE) inhibitors: **captopril**, **enalapril**, ramipril Calcium channel blockers: nifedipine, amlodipine Others: **methyldopa**, diazoxide, prazosin, doxazosin
Antimalarials	**Chloroquine**, **hydroxychloroquine**, **mepacrine**
Antimicrobials	Tetracyclines, sulfamethoxazole, griseofulvin, isoniazid, streptomycin, ethambutol, pyrazinamide
Heavy metals	**Gold salts**, mercury, arsenic, antimonials
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Naproxen, aspirin, ibuprofen, indomethacin
Hypoglycemic agents	Chlorpropamide, tolazamide, tolbutamide
Diuretics	Chlorothiazide, hydrochlorothiazide, furosemide
Tumor necrosis factor (TNF)-α inhibitors/ biologics	**Etanercept**, **infliximab**, adalimumab, lenercept, anakinra, imatinib, rituximab
Anticonvulsants and antipsychotics	Carbamazepine, phenytoin, chlorpromazine, amitriptyline, imipramine, lorazepam, lithium, trihexyphenidyl
Miscellaneous	**Penicillamine**, **quinidine**, allopurinol, dapsone, hydroxyurea, procainamide, levamisole, omeprazole, simvastatin, pravastatin

Those marked in bold are more commonly associated.

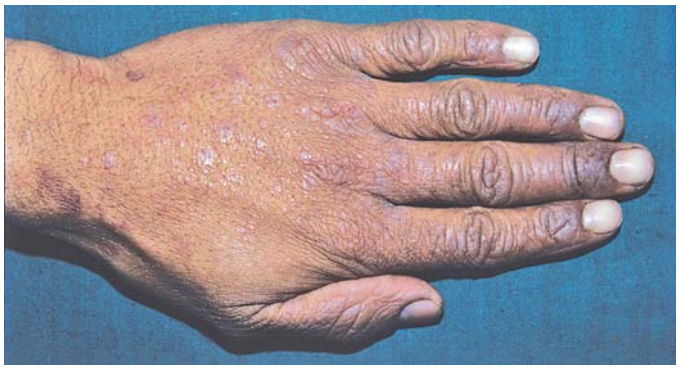

Fig. 15.1: Lichenoid eruption in a studio worker. (Courtesy of Dr. M. Ramam, New Delhi.)

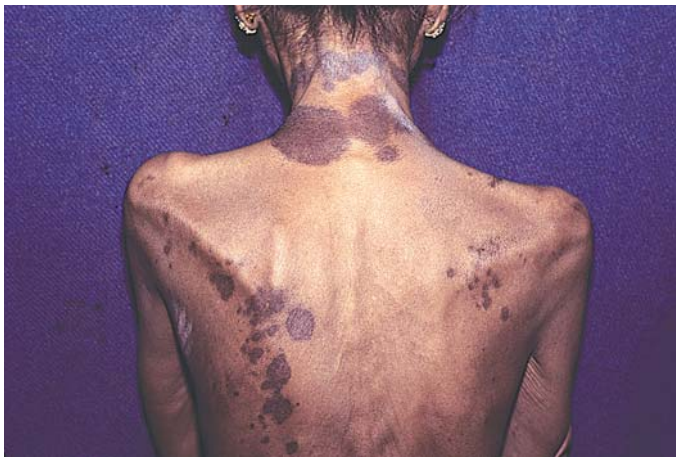

Fig. 15.2: Lichenoid eruptions due to Gold in a patient of rheumatoid arthritis. (Courtesy of Dr. M. Ramam, New Delhi.)

and a significant correlation has been found between CD8 frequency and perforin expression in skin histology from LDR versus classical LP. A possibility of cross-reactivity of herpes simplex virus (HSV)–specific antiviral skin-resident CD8 memory cells with drug, inducing LDR, has been suggested.[13] Some of the other postulated mechanisms include inhibition of prostaglandin synthesis causing epidermal alterations (NSAIDs), alternation in extracellular signal kinases pathways that affect keratinocyte migration (β-blockers), and upregulation of precursor cytokines such as interferon α that may elicit a subsequent inflammatory response causing LDR.[14]

CLINICAL FEATURE

The lesions usually exhibit typical morphology of LP, but tend to be more generalized, present symmetrically over trunk (Figs. 15.3 A and B) and extremities (Fig. 15.4), without any preference for the flexures. Itching is variable but usually severe and intense. Eczematous, pityriasiform, and psoriasiform (Fig. 15.5) morphology may also be seen. Wickham's striae, oral and nail lesions are less commonly seen than idiopathic LP. Photodistributed (Fig. 15.6), ulcerated, bullous, follicular, linear lesions have been described. Lesions resembling oral LP may sometimes be seen in the oral cavity, in the areas adjacent to contact with dental amalgam material (Fig. 15.7) that usually resolve after removal of dental amalgams. Certain features that favor LDR and may help to differentiate it from idiopathic LP are provided in Table 15.2.

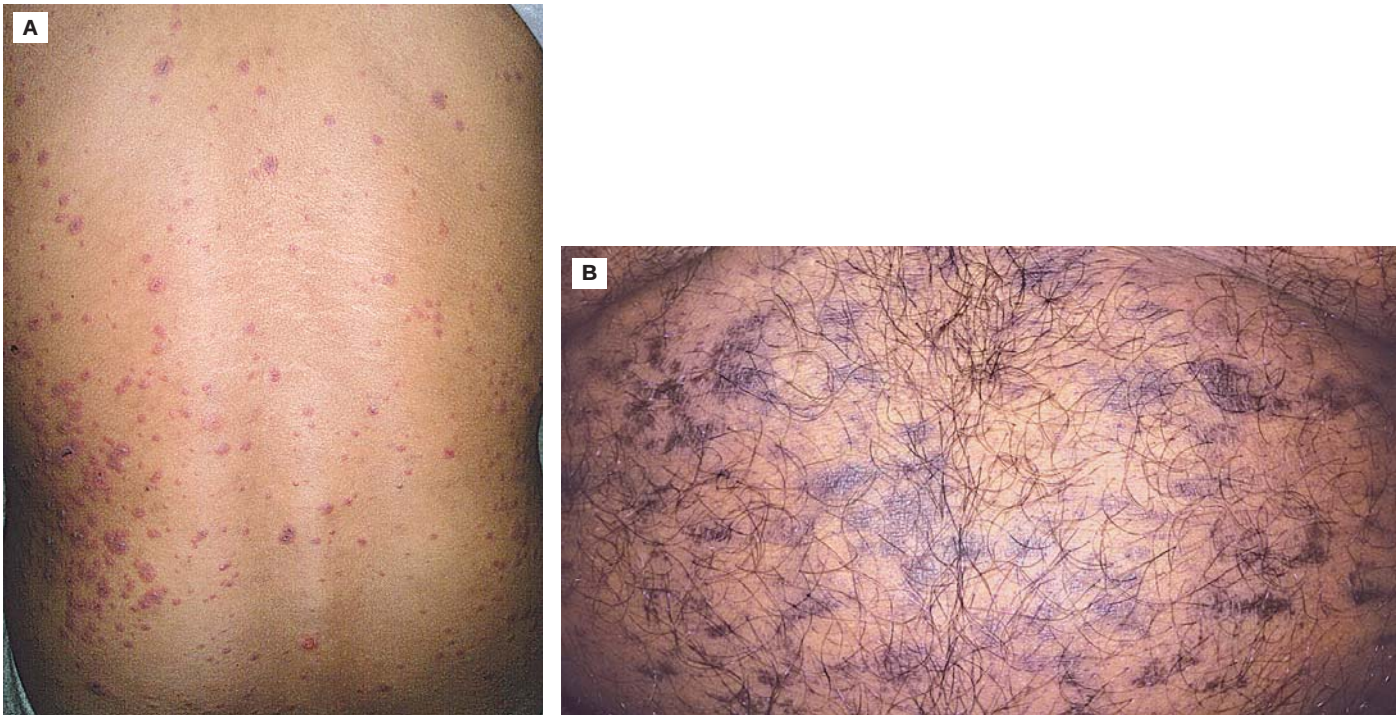

Fig. 15.3: (A) Lichenoid rash on trunk in a patient taking amlodipine for last 3 months; (B) Lichenoid drug eruption developing in a patient after Rituximab for lymphoma. (Fig. B, Courtesy of Dr. Brijesh Nair, Kochi.)

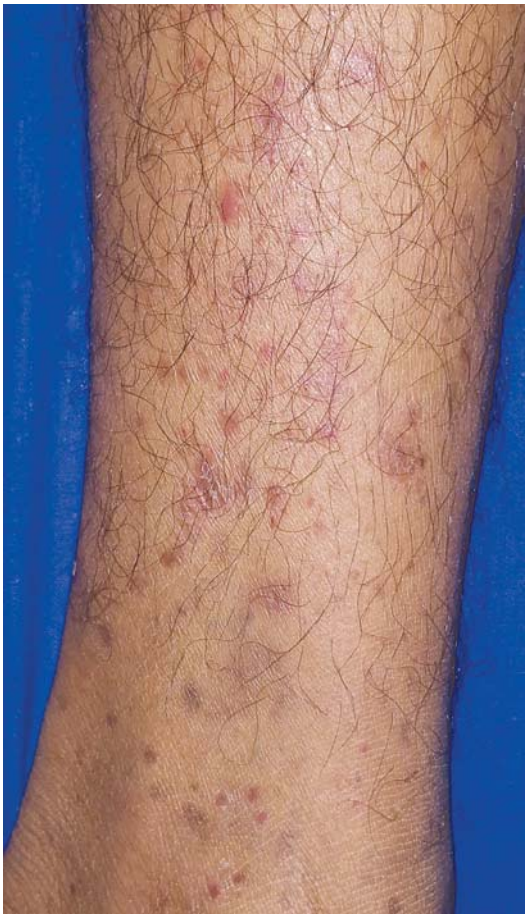

Fig. 15.4: Lichenoid lesions on leg in a patient on furosemide.

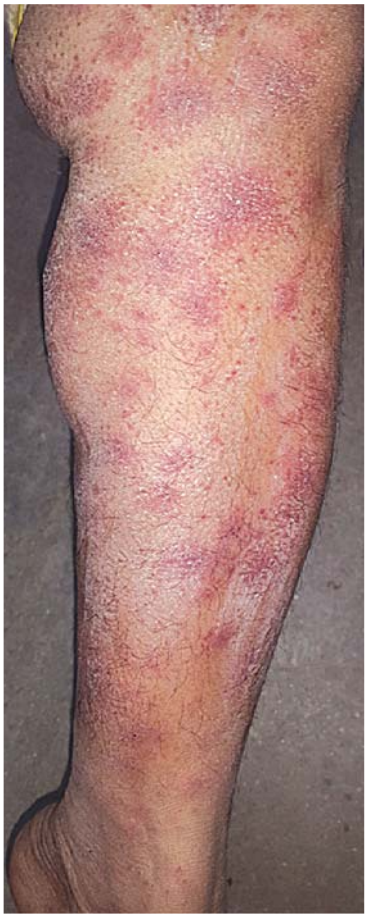

Fig. 15.5: Chloroquine induced lichenoid rash with psoriasiform morphology. (Courtesy of Dr. R.D. Mehta, Bikaner.)

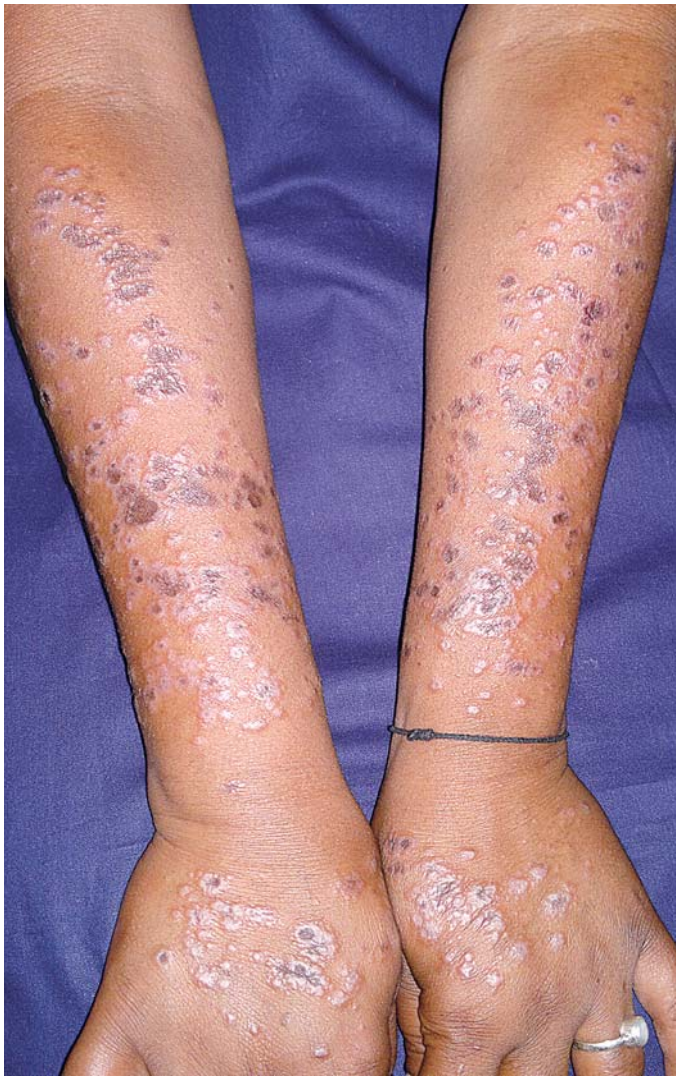

Fig. 15.6: lichenoid rash in photodistribution in patient on carbamazepine.

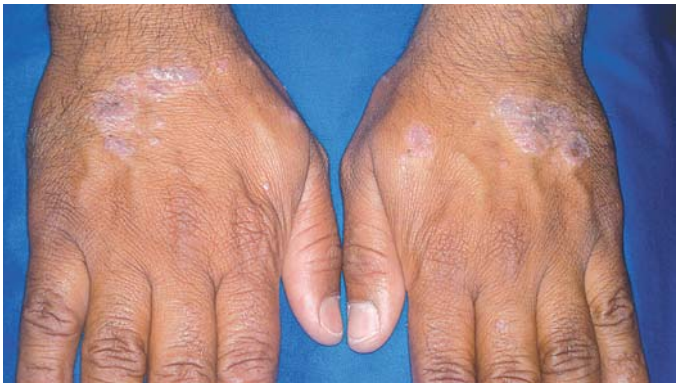

Fig. 15.7: Photosensitive lichenoid rash due to griseofulvin.

Table 15.2: Features helpful in distinguishing LP from LDR

	LP	LDR
Trigger	Unknown	Drugs
Latent period	Unknown	Few weeks to 2 years
Distribution	Flexural, genitalia	More generalized, often spares classical LP sites/often photodistributed
Morphology	Shiny, polygonal, flat topped, violaceous	More polymorphous rash—eczematous, psoriasiform, or pityriasis rosea like
Wickham's striae	Present	Uncommon
Mucosal and nail involvement	Very common	Uncommon
Histology	Parakeratosis absent Presence of eosinophils and plasma cells usually absent Necrotic keratinocytes absent	May be seen More pleomorphic infiltrate with presence of eosinophils and plasma cells Necrotic keratinocytes may be seen in clusters in epidermis
Response to treatment	Shorter course, improves with super-potent topical corticosteroids	Protracted course, response to topical corticosteroids less remarkable

HISTOPATHOLOGY

There is no single histological feature that can differentiate idiopathic LP from LDR.[4,15] Direct immunofluorescence findings[16] are also similar. Both show an interface dermatitis with subepidermal band–like infiltrate. However, some features that are suggestive of LDR include the following:

1. Focal hyperkeratosis
2. Focal interruption of the granular layer
3. Dyskeratotic keratinocytes (cytoid bodies) in cornified and granular layer
4. Eosinophils and plasma cells in the dermal infiltrate
5. Others: Atrophy of epidermis, exocytosis of lymphoid cells in upper layer of epidermis, and infiltrate around deep dermal vessels

"Granulomatous lichenoid dermatitis" or giant cell lichenoid dermatitis is a newly described[17] histological entity, usually drug induced, characterized by a lichenoid dermatitis and a granulomatous infiltrate composed of histiocytes and multinucleated giant cells. Infiltration of hair follicles and eccrine structures may also be seen. The causative drugs include antibiotics, ACE inhibitors, β-blockers, lipid-lowering agents, phenolphthalein and NSAIDs.

MANAGEMENT

A meticulous drug history including prescriptional and over-the-counter medications and their temporal relationship with occurrence of lichenoid rash may be helpful in pinpointing the suspected drug(s). Ascertaining the exact causal drug(s), however, may be difficult at times if patient is on multiple medications as is usually the case and also because LDR may continue to develop even after stoppage of drug. Rechallenge may also be impractical due to long latency of LDR. Though patch testing and in vitro tests (lymphocyte stimulation and macrophage migration inhibition test) have been done to identify the culprit agent, they remain of limited value in confirming the diagnosis.[4] The decision to discontinue the drug(s) depends on the benefit of resolving the rash and availability of an effective and safer alternative to treat the primary condition. The drug may also be terminated and then restarted after the skin lesions have disappeared, with a careful monitoring. Discontinuation of suspected agent may lead to resolution of rash after a variable but prolonged period ranging from weeks to months, unlike urticarial or exanthematous drug rash that subsides soon after the culprit drug is stopped.

Topical steroids may offer some benefit, but the response is relatively less remarkable than in idiopathic LP, and this has been suggested as a pointer in the favor of diagnosis of LDR.[14]

Antihistamines and short course of systemic corticosteroids may be used depending on the severity of reaction.

LEARNING ESSENTIALS

- It is important to differentiate LDR from idiopathic LP due to the difference in the treatment strategy, which essentially involves withdrawal of suspected drug in LDR.
- Some drugs causing LDR are gold salt, antimalarials, penicillamine, β-blockers, and ACE inhibitors. Biological agents may also paradoxically cause LDR.
- Lichenoid drug reactions tend to be more extensive, polymorphic, and symmetric without any flexural predilection. The involvement of mucosae and nails is relatively infrequent.
- A long latency in appearance of rash after initiation of drug and delayed resolution upon drug stoppage are characteristically noted in LDR.

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Chapter

16

Drug Induced Pityriasis Rosea–Like Rash, Psoriasiform Rash and Erythroderma

Sudha Agarwal • Paschal D'Souza

SUMMARY

Drug eruptions causing cutaneous lesions resembling idiopathic pityriasis rosea (PR), psoriasis, and erythroderma are being increasingly reported more due to the increased awareness of this possibility rather than their clinically distinct features. Development of a de novo eruption in any patient on single or multiple medications should be suspected as drug induced even though it resembles well-defined dermatoses like PR or Psoriasis or nonspecific condition like erythroderma. Few of the features suggestive of drug-induced cutaneous eruption could be the following:

1. Absence of herald patch, more itchy, inflammatory, and coalescing lesions with acral involvement along with truncal lesions could be drug-induced PR. Tissue and peripheral eosinophilia may be present.
2. Eruptions clinically resembling psoriasis in a patient on known offending drugs may be drug-induced or drug-aggravated psoriasis. Helpful features on histology are the absence of tortuous papillary dermal capillaries and related suprapapillary epidermal thinning and presence of perivascular or interstitial eosinophils in the upper dermis.
3. Rapid onset of generalized erythema and exfoliation beginning in a local fashion or a sudden onset of exfoliation in a patient with no past history of any skin disorder but who is on medication for last 2–12 weeks could be drug-induced erythroderma. Other helpful features are large scales, accompanying facial edema, and dependent purpura.

PITYRIASIS ROSEA–LIKE DRUG ERUPTION

Pityriasis rosea (PR) is a benign, self-limiting cutaneous eruption that begins with a "herald patch", in 50%–90% of cases. The secondary eruption, in which numerous papulosquamous lesions develop in crops over a period of 1–2 weeks, occurs 2–21 days later. A characteristic feature is the collarette appearance of the scale, with edges peripherally attached and lifted up near the center of the lesion. The distribution of the lesions is usually bilateral and produces the classic "Christmas tree" pattern on the trunk. An almost similar eruption to PR has been attributed to several drugs especially if it is atypical, severe and protracted.

ETIOLOGY

PR-like eruptions (Fig. 16.1) have been reported to occur in association with many drugs[1,2] (Table 16.1).

PATHOGENESIS

Exact cause of PR-like drug eruption for the several reported drugs is not known. Some of the hypotheses put forward are the following:

1. Presence of increased levels of arachidonic acid leading to leukotriene release causing cutaneous inflammation in cases of NSAIDS.[3]
2. Increased kinin levels evoking cutaneous inflammation in case of Angiotensin-converting enzyme (ACE) inhibitors.[4]
3. Metabolites produced during liver metabolism in case of clozapine.[1]
4. Reactivation of viral infections on account of lowered immunity in case of biologics. It could also be a manifestation of immune response to presence of tumor necrosis factor (TNF)-α antibodies in patients on biologics.

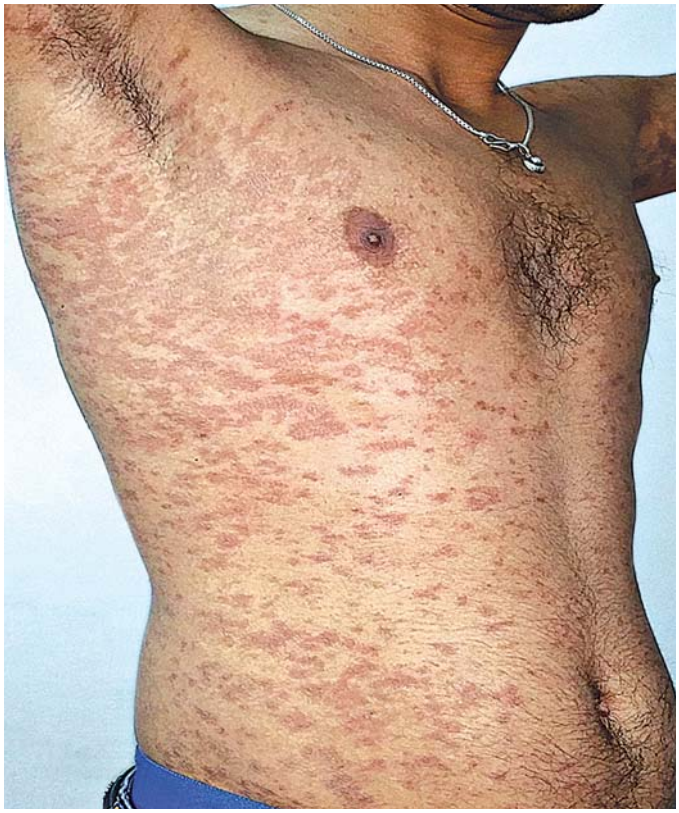

Fig. 16.1: Extensive papulosquamous rash with pityriasis rosea like morphology in a patient on metronidazole.

Table 16.1: List of drugs reported to cause PR-like eruption

Drug category	Examples
NSAIDs	Acetylsalicylic acid, nimesulide
Antihypertensives	Captopril, clonidine
GIT related	Loperamide, metronidazole, omeprazole, levamisole
Psychiatric	Lithium, barbiturates, nortriptyline, clozapine, methoxypromazine
Biologics	Adalimumab, etanercept and rituximab
Vaccines	Bacille Calmette–Guérin (BCG), human papilloma virus, diphtheria, pneumococcal, Hepatitis B vaccine and H1N1 vaccine
Antiacne	Isotretinoin
Gout treatment	Allopurinol
Antifungal	Terbinafine
Antihistamine	Pyribenzamine, ketotifen
Antineoplastic	Imatinib mesylate
Miscellaneous	Bismuth, gold, mustard oil, arsenicals, ergotamine tartrate, D-penicillamine

NSAIDs - nonsteroidal anti-inflammatory drugs; GIT - gastrointestinal tract.

5. Induction of general inflammatory response in case of vaccines. Vaccines may also act as mimickers of the causative virus responsible for idiopathic PR.[5]
6. The inhibition of c-Kit and/or platelet-derived growth factor receptor (PDGFR) tyrosine kinase activity in basal epidermal keratinocytes, melanocytes, tissue mast cells in case of antineoplastic drug imatinib mesylate may cause the eruption as a pharmacological effect.[6]

HOW TO SUSPECT A PR-LIKE DRUG ERUPTION?

As mentioned, most cases of PR-like drug eruptions probably pass unnoticed because they behave in the same benign self-limited way as idiopathic PR. Table 16.2 lists the clues which should make one suspect a drug etiology.[1–2,6–11]

DIFFERENTIAL DIAGNOSIS

Apart from the idiopathic PR, some other dermatoses may need to be considered in a case of drug-induced PR-like eruption:

- **Guttate Psoriasis**: May present with erythematous few millimeter lesions in extensive crops over trunk in children and young adults. There may be history of upper respiratory tract infection. The pink color of the lesions and the silvery scale may give a clue.
- **Lichenoid eruption**: Lesions may resemble lichen planus with flat topped, itchy, violaceous papules and a tendency to involve the flexures and extremities.
- **Secondary Syphilis**: Copper colored, nonpruritic, truncal rash in a sexually active patient with involvement of palms and soles and lymphadenopathy should call for investigations. A rapid plasma reagin or VDRL test will give clue to the diagnosis.
- **Seborrheic dermatitis**: Pityriasiform variant of seborrheic dermatitis may have superficial resemblance. However greasy, scaly lesions with a predilection for scalp, centrofacial area, midline of trunk, and genitalia are also seen.
- **Nummular Eczema**: Can present with round to oval itchy lesions. They are usually papulovesicular and acral and seen mainly over the shins, dorsa of hands and feet.
- **Pityriasis lichenoides chronica**: They also present with multiple erythematous papules over trunk without a herald patch and have a prolonged chronic course. The lesions are in varying states of evolution with single mica-like removable scale and simultaneous areas of postinflammatory hypopigmentation.

Table 16.2: Differences between idiopathic PR and PR-like drug eruptions

Clues	Pityriasis rosea	PR-like drug eruption
Historical clues	• Appearance of symmetrical truncal eruption in otherwise healthy children or young adults often following an upper respiratory tract infection which is usually preceded by a single larger herald patch.	PR-like eruption in: • A middle-aged or elderly patient on drugs for any underlying condition.
Circumstantial clues	Presence of: • Seasonal preponderance • Clustering of cases • Prodromal symptoms • A positive history of preceding upper respiratory infection	Absence of: • Seasonal preponderance • Clustering of cases • Prodromal symptoms • History of preceding upper respiratory infection
Clinical clues	• Preceding herald patch • Papulosquamous round to oval lesions with collarette scaling, usually bilateral and symmetrical producing classic "Christmas tree" pattern on the trunk, generally discrete and salmon pink in color. • Characteristic truncal involvement with minimal involvement of extremities. • Absence or minimal itching in lesions • Absence of mucosal lesions	• No preceding herald patch • Similar or papular, vesicular and even pustular lesions. Tendency of lesions to coalesce and become confluent. Inflammation may be pronounced with lesions tending to be bright violet-red. • Greater involvement of extremities along with characteristic truncal involvement • Presence of severe itching not responsive to oral antihistamines • Presence of oral mucosal lesions
Histological clues	H&E: • Epidermis shows parakeratosis, acanthosis, spongiosis, lymphocyte exocytosis. Dermis shows superficial perivascular dermatitis with inflammatory infiltrate mainly composed of lympho-monocytes, few eosinophils along with extravasation of red blood cells into the superficial dermis. Cell typing: • Both epidermal and dermal lymphocytes are of CD4+ type.	H&E: • Similar features. In addition there may be scattered necrotic keratinocytes, and vacuolar alteration of keratinocytes in the basal layer of the epidermis. In dermis marked edema of the papillary with frequent eosinophils. Cell typing: • Intraepidermal lymphocytes primarily CD8+ T cells, whereas dermal perivascular and interstitial lymphocytes primarily CD4+ T cells.
Other laboratory clues	• Absence of peripheral eosinophilia • Presence of evidence of HHV 6 and HHV 7 DNA activation in plasma and blood mononuclear cells.	• Presence of peripheral eosinophilia • Absence of evidence of HHV 6 and HHV 7 DNA activation in plasma and blood mononuclear cells.
Evolutionary clues	• Lesions usually resolve completely in 6–8 weeks	• Persistence of rash while patient on the suspected medication • Rapid resolution of eruptions within 5–15 days of drug withdrawal

H&E - hematoxylin and eosin; HHV - human herpesvirus.

TREATMENT

As most of the time drug-induced PR is mild, and behaves like the self-limiting idiopathic disease, treatment is conservative and begins with identification and withdrawal of the drug wherever possible. Symptoms usually dramatically resolve within 5–15 days. General patient education regarding avoidance of exposure to irritant agents (e.g. harsh soaps, fragrances, extremes of water temperature, wool, and synthetic fabrics), wearing comfortable, loose cotton clothing, and abstaining from scratching the severely pruritic skin may help. For itchy skin, topical preparations containing bland emollients, calamine, menthol–phenol, pramoxine, colloidal starch, or oatmeal may be useful. In case

of severity, topical steroids/antibiotic combinations can be applied to take care of the microabrasions. Oral antihistamines, including sedative ones should be given as drug-induced PR can be very itchy and does not respond to conventional antihistamines.

PSORIASIFORM DRUG ERUPTION

INTRODUCTION

Psoriasiform drug eruptions are cutaneous drug eruptions simulating psoriasis clinically and/or histologically and typically consist of erythematous plaques surmounted by large dry silvery scales. A number of drugs can exacerbate preexisting psoriasis, induce new lesions on clinically normal skin in patients with psoriasis, or precipitate psoriasis in individuals with or without a family history of psoriasis.[12,13]

ETIOLOGY

Drugs that may cause psoriasiform eruptions or exacerbate psoriasis are listed in Table 16.3.

Table 16.3: List of drugs reported to cause psoriasiform eruption

Most commonly associated drugs	β-blockers Lithium Antimalarials (chloroquine and hydroxychloroquine)
Other associated drugs	Antibiotics: Tetracycline Nonsteroidal anti-inflammatory agents ACE inhibitors Interferons Terbinafine Benzodiazepines
Less commonly associated drugs	Digoxin Clonidine Amiodarone Quinidine Gold TNF-α inhibitors Imiquimod Fluoxetine Cimetidine Gemfibrozil

Source: Tsankov et al.[12]; Kim and Del Rosso[14].

PATHOGENESIS

Psoriasiform reactions are elicited by inflammatory events that cause dysregulation of cytokines, growth factors, and abnormal keratinocyte proliferation.

β-Blockers

Theories proposed regarding the pathogenesis of β-blocker-induced psoriasis include a delayed type hypersensitivity reaction, impaired lymphocyte transformation, decrease in the intraepidermal cyclic adenosine monophosphate (cAMP) levels.[15,16] The latter is an intracellular messenger that is responsible for the stimulation of proteins for cellular differentiation and inhibition of proliferation. Both groups of β-blockers are also responsible for excessive release of enzymes by lymphocytes, neutrophils, and macrophages, which is believed to be responsible for the presence of hyperproliferation and psoriasiform change.

Lithium

Lithium can cause psoriasis in susceptible patients or aggravate existing psoriasis. Among the mechanisms described are depletion of inositol monophosphatase resulting in alterations in calcium homeostasis and serotonergic function.[17] Low intracellular calcium levels due to lithium cause increased proliferation of keratinocytes and affect terminal differentiation. In addition, lithium increases the production of interleukin-2 (IL-2), TNF-α and interferon-γ in psoriatic keratinocytes.[15,18]

Antimalarials

Antimalarials (AMs) causes inhibition of transglutaminase in the skin, which is thought to influence cellular proliferation and can provoke de novo pustular psoriasis.[15]

Antibiotics

Tetracyclines can cause psoriasis through reduction of intracellular cAMP and by the interaction with arachidonic acid and its metabolites.[19]

Nonsteroidal Anti-inflammatory Drugs

NSAIDs inhibit the metabolism of arachidonic acid by the cyclo-oxygenase (COX) pathway leading to accumulation of leukotrienes, which has been postulated to aggravate psoriasis.[15]

ACE Inhibitors

Recent studies suggest that patients with a history of familial psoriasis and a specific ACE genotype exhibiting low ACE activity are more susceptible to developing psoriasis after initiation of therapy.[20]

CLASSIFICATION OF PSORIASIFORM DRUG ERUPTION

Psoriasiform drug eruption is divided into two categories (Box 16.1). The first category is exacerbation of preexisting psoriasis and development of psoriatic lesions on uninvolved skin in patients with psoriasis,

Box 16.1: Categories of psoriasiform drug eruptions

Drug-aggravated psoriasis

- Psoriasis-like eruption continues even after the offending drug is withdrawn.
- Usually occurs in background of positive family history or a genetic predisposition for psoriasis.
- Presents as flare up of pre-existing psoriatic lesions or the development of new psoriatic lesions in previously uninvolved skin.

Drug-induced psoriasis

- Withdrawal of the causative drug arrests progression of the disease.
- Eruptions appear de-novo with no previous history and/or family history of psoriasis.

where the disease progresses even after the discontinuation of the offending drug. The second category includes precipitation of psoriasis de novo in patients with no predisposition and family history of psoriasis, and where discontinuation of the causative drug stops the further progression of the disease.[12]

HOW TO SUSPECT DRUG-INDUCED / AGGRAVATED PSORIASIS?

A high index of suspicion is required to pick up cases of drug-induced or aggravated psoriasis as it closely mimics idiopathic form in the spectrum of clinical presentation. Helpful features are mentioned in Table 16.4.[21–25]

Table 16.4: Clues suggestive of psoriasiform drug rash

Clues	Comments
Latency period	Latency period of drugs inducing or aggravating psoriasis may be: • Short, i.e. around 4 weeks (NSAIDs and terbinafine) • Intermediate, i.e. 4–12 week (antimalarial agents and ACE inhibitors) • Long, i.e. 12 weeks (lithium and beta-blockers) A paradoxical adverse psoriasiform cutaneous reaction has been documented with interferon-α and the anti-TNF agents infliximab and etanercept. All interferons may exacerbate psoriasis, but only interferon-α induces de novo psoriasis.
Clinical features	Psoriasiform lesions appear morphologically similar to the prototypic classical psoriasis (Fig. 16.2). Clinical spectrum includes limited or generalized erythematous plaques with thick, large, silvery scales, erythroderma or pustular lesions. Clinical improvement after withdrawal of the implicated drug and recurrence within a few days of reexposure suggests drug etiology. Clinically psoriasiform lesions are less red, thick, or scaly than the classic lesions and spare knee and elbow.
Histopathological features	Very similar to those of psoriasis with psoriasiform epidermal hyperplasia, neutrophils within parakeratosis, diminution of the stratum granulosum, and superficial perivascular lymphocytes (Fig. 16.3). A helpful feature distinguishing drug-induced from idiopathic psoriasis is the absence of tortuous papillary dermal capillaries and related suprapapillary epidermal thinning and more frequently presence of perivascular or interstitial eosinophils in the upper dermis. On IHC, stain for CD123, a PDC marker shows positivity in the perivascular infiltrate in the upper dermis. CD4+ T-cells in the epidermis are less and CD8+ more frequently seen in psoriatic epidermis than in psoriasiform lesions. Similarly in the upper dermis positivity of CD4+ T-cells is less and CD8+ more in psoriasis in comparison to psoriasiform lesion.
Other laboratory findings	Presence of peripheral eosinophilia suggests drug etiology of eruption.
Evolution of the lesions	Lesions begin to improve within days of drug withdrawal without the need for specific treatment specially in drug-induced psoriasis and usually clear within weeks. Reexposure with oral challenge results in recurrence within a few days. Favorable response to drug withdrawal not seen in cases of drug-aggravated psoriasis where lesions can persist even after drug withdrawal.

IHC - immunohistochemistry; PDC - plasmacytoid dendritic cell.

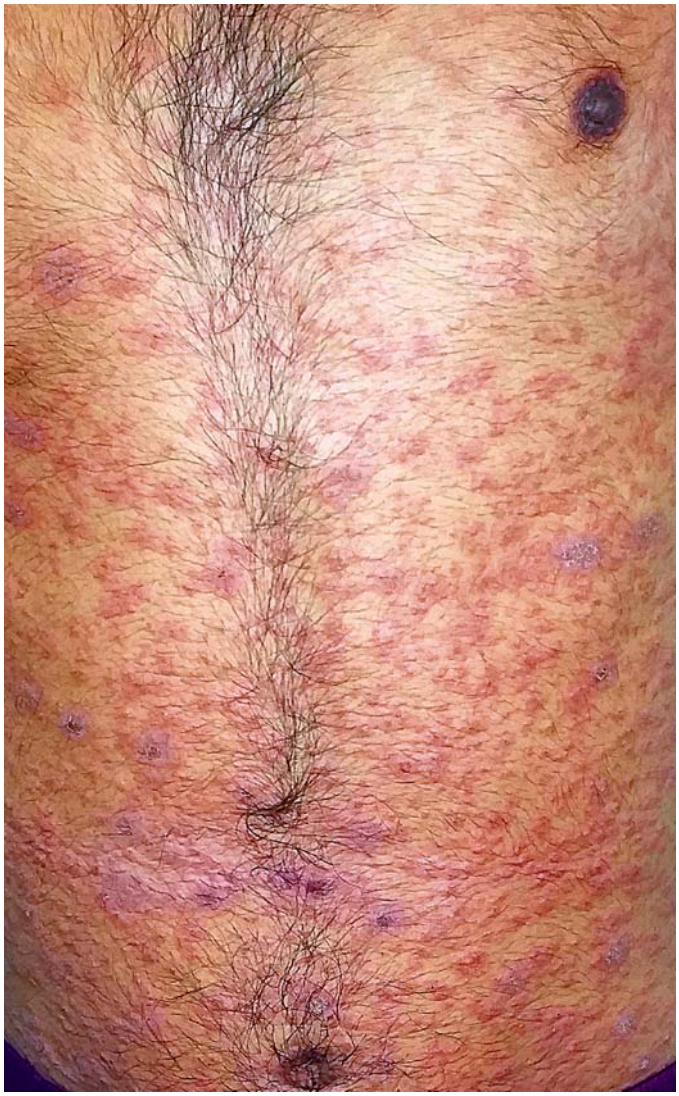

Fig. 16.2: Psoriasiform drug eruption induced by lithium.

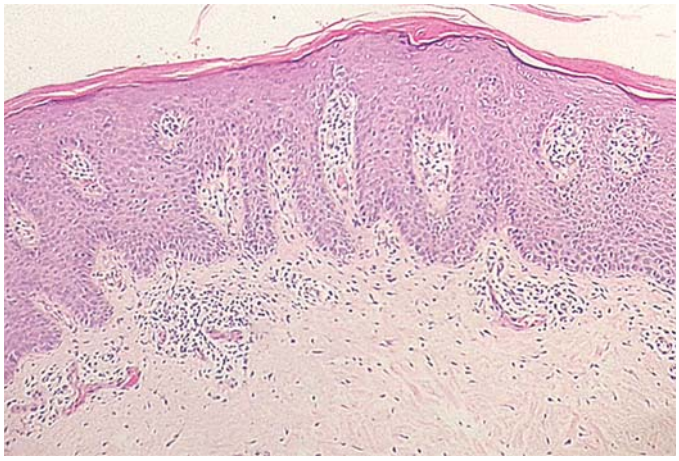

Fig. 16.3: Skin biopsy specimen shows psoriasiform epidermal hyperplasia with hyperkeratosis, confluent parakeratosis, and hypogranulosis with some capillary proliferations at the tips of the dermal papillae, and a perivascular lymphocytic infiltrate with a few eosinophils in the upper dermis [Haematoxylin and Eosin (H&E) × 100].

DIFFERENTIAL DIAGNOSIS

Apart from the idiopathic psoriasis, the followings dermatoses may be considered in a case of psoriasiform drug eruption:

- **Nummular eczema**: Can present with round to oval itchy lesions. They are usually papulovesicular and acral and seen mainly over the shins, dorsa of hands and feet.
- **Pityriasis lichenoides chronica**: They also present with multiple erythematous papules over trunk without a herald patch and have a prolonged chronic course. The lesions are in varying states of evolution with single mica-like removable scale and simultaneous areas of post inflammatory hypopigmentation.
- **Secondary syphilis**: Copper colored, nonpruritic, papules and plaques in a sexually active patient with involvement of palms and soles and lymphadenopathy should call for investigations. A rapid plasma reagin or VDRL will give clue to the diagnosis.
- **Lichen simplex chronicus**: Localized, well-circumscribed lichenified plaques with a predilection for the back and sides of the neck, the scalp, the upper eyelid, the orifice of one or both ears, the palm, soles, or often the wrist and ankle flexures.

TREATMENT

In psoriasiform eruptions, lesions begin to improve within days without the need for specific treatment, and lesions have usually cleared within weeks after discontinuation of the drug alone. This can cause rapid regression of the disease. If lesions are present only in localized areas, emollients alone can be helpful. Topical treatments such as corticosteroids or calcipotriol may accelerate resolution.

Drug-associated or drug-exacerbated psoriasis improves upon discontinuation of medication, but usually does not completely resolve and need topical corticosteroids, keratolytics, vitamin D analogues, oral retinoids, psoralen plus ultraviolet A (PUVA) therapy, and methotrexate and systemic agents as used in the treatment of idiopathic psoriasis.

DRUG-INDUCED EXFOLIATIVE DERMATITIS

INTRODUCTION

Exfoliative dermatitis, also known as erythroderma, is an uncommon but serious skin disorder, which results in intense generalized redness of the skin with scaling of the skin involving more than 90% of the body surface. First described by Von Hebra in 1868,[26]

it may be drug induced, idiopathic, or secondary to underlying cutaneous or systemic disease or malignancy.[26,27] It is of great concern because it is one of the few dermatological emergencies having significant risk of morbidity and mortality owing to dysmetabolism and its complications. This disorder in addition carries the risks inherent to the underlying disease and its therapy.

ETIOLOGY OF DRUG-INDUCED ERYTHRODERMA

Theoretically, any drug may cause exfoliative dermatitis; however, drugs commonly causing exfoliative dermatitis are given in Box 16.2.[27–31]

Box 16.2: List of common drugs reported to cause exfoliative dermatitis

- Allopurinol
- Antimicrobials: Cephalosporins, penicillins, chloramphenicol, erythromycin, gentamicin, amphotericin, antituberculous drugs, nalidixic acid, nitrofurantoin, sulfonamides
- Barbiturates
- Captopril
- Carbamazepine
- Furosemide
- Gold salts
- Lithium
- Phenothiazines
- Phenylbutazone
- Phenytoin
- Thiazides

PATHOGENESIS

The pathophysiologic processes resulting in exfoliative dermatitis vary with the underlying disorder. However, common to all conditions that cause exfoliative dermatitis, there is an increased rate of skin turnover, decreased epidermal transit time, overall greater loss of epidermal material, which is manifested clinically as severe scaling and shedding. This results in loss of proteins, amino acids, and nucleic acids, which may cause a negative nitrogen balance.[31] The amount of scale lost varies by underlying condition and its severity.

Exfoliative dermatitis due to drug reactions may result in the loss of 7.2 g of scale per day (normal range, 500–1000 mg). Protein lost in that scale is 4.2 g per day.[32] The decreased transit time also results in impaired skin barrier function from incomplete keratinization, which may increase the absorption of medications administered transcutaneously through damaged skin.

Another common pathophysiologic process to all forms of exfoliative erythroderma is increased blood flow to the skin, which, in combination with impaired skin barrier function, results in increased insensible fluid loss through transpiration. Dehydration and reflex tachycardia are common. In severe cases, high-output cardiac failure may occur. Increased cutaneous blood flow also leads to increased heat loss, which may lead to a compensatory hypermetabolism and cachexia.

It has been found that complicated interaction of cytokines and cellular adhesion molecules: IL-l, IL-2, and IL-8 interact with intercellular adhesion molecule 1 (ICAM-1) cause increased epidermal turnover rate.[26] TNF and interferon-γ are the cytokines that may have roles in the pathogenesis of exfoliative dermatitis, as they stimulate dermal inflammation, epidermal proliferation, and increased production of inflammatory mediators.

CLINICAL MANIFESTATIONS

The first stage of exfoliative dermatitis is erythema, often beginning as single or multiple pruritic patches, which increase in size and coalesce to form extensive areas of erythema, involving especially the head, trunk, and genital region, and eventually spread to involve most of the skin surface (Figs. 16.4 and 16.5).[26] Usually, but not always, the palms, the soles and the mucous membranes are spared. The nose and paranasal area may be spared, which is known as "nose sign."[33] White or yellow scales inevitably develop that progress to give the skin a dry appearance with a dull scarlet and gray hue. Induration and thickening of the skin from edema and lichenification may provoke a sensation of severe skin tightness in the patient. The skin is bright red, dry, scaly, and warm to touch.

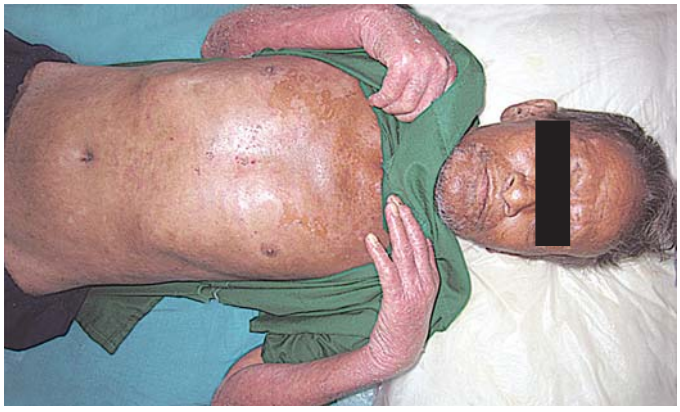

Fig. 16.4: Isoniazid-induced exfoliative dermatitis; Erythematous scaly plaques on trunk and upper extremities.

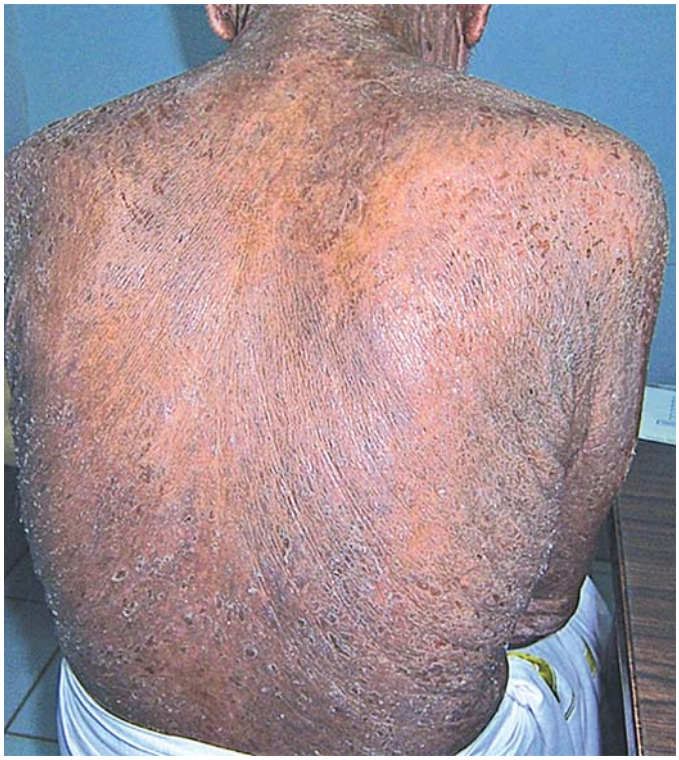

Fig. 16.5: Carbamazepine induced erythroderma in an elderly male.

The exfoliative process sometime may involve the palms and soles, with hair loss and nail shedding. Involved nails are thick, lusterless, dry, brittle, and show ridging of the nail plate. Subungual hyperkeratosis, distal onycholysis, splinter hemorrhages occur; and sometimes, the nails may shed. Alternating bands of nail plate discontinuity and leukonychia may be seen in drug-induced erythroderma.[26,28,30]

The most frequently noted symptoms in patients with exfoliative dermatitis include malaise, pruritus, and a burning sensation. Both hyperthermia and hypothermia are reported. Other clinical findings include lymphadenopathy, hepatomegaly, splenomegaly, edema of the foot or ankle, and gynecomastia.

The scaling that occurs in exfoliative dermatitis can have severe metabolic consequences, on account of which the body loses heat, water, protein, and electrolytes, and renders itself much more vulnerable to infection.

Heat loss is another major concern that accompanies a defective skin barrier in patients with exfoliative dermatitis. Loss of normal vasoconstrictive function in the dermis, decreased sensitivity to the shivering reflex can all result in thermoregulatory dysfunction that can cause hypothermia or hyperthermia. The basal metabolic rate also is increased in patients with exfoliative dermatitis. A catabolic state thus ensues, which is often responsible for significant weight loss.

Each of these physiologic disruptions is potentially life threatening. Hypothermia can result in ventricular flutter, decreased heart rate, and hypotension. Increased peripheral blood flow can result in high-output cardiac failure. Hypervolemia can also occur in patients with exfoliative dermatitis, contributing to the likelihood of cardiac failure.

HOW TO SUSPECT A DRUG-INDUCED EXFOLIATIVE DERMATITIS?

As drug eruption is one of the important causes of exfoliative dermatitis, so a thorough medication history is mandatory. The following manifestations could be suggestive of a drug-induced exfoliative dermatitis (Table 16.5).

DIFFERENTIAL DIAGNOSIS

Clinical clues for other common causes of exfoliative dermatitis:

- **Psoriasis**: Medical history or family history of psoriasis, withdrawal of corticosteroids, methotrexate, or cyclosporine, sparing of face, nail pitting, translucent yellow-red nail bed discoloration, onycholysis, inflammatory arthritis.
- **Atopic dermatitis**: Past medical or family history of atopy, severe pruritus, flexural skin being most severely affected, lichenification and prurigo nodularis.
- **Idiopathic**: Elderly, severe pruritus, chronic and relapsing course palmoplantar keratoderma and dermatopathic lymphadenopathy.
- **Staphylococcal scalded skin syndrome**: Acute exfoliation of the skin typically following a generalized erythema with tenderness of the skin.

COURSE AND PROGNOSIS

The course of exfoliative dermatitis is greatly influenced by etiology. Drug-induced exfoliative dermatitis has the best prognosis among all the causes of exfoliative dermatitis often resolving in 2–6 weeks. The most common causes of death in patients with erythroderma are pneumonia, septicemia, and heart failure.

TREATMENT

Early recognition, prompt withdrawal of drug is the cornerstones of management of drug-induced exfoliative dermatitis. Hospitalization is indicated in most cases to ensure that the necessary cutaneous, laboratory, and radiologic investigations are performed. Typically, symptoms resolve within 2–6 weeks after cessation of the offending agent.

Table 16.5: Clues suggestive of drug-induced erythroderma

Clues	Comments
Historical	• Localized exanthem followed by generalization is more common with topical medications. • A recent history of a morbilliform or scarlatiniform eruption is common with oral medications. • Absence of past history of skin disease. • Medical history includes one of implicated drugs taking within 2–12 weeks.
Clinical	• Rapid clinical evolution of the disease, followed by rapid resolution if the offending agent is removed. • Scale usually large in drug eruptions compared to fine in atopic dermatitis and dermatophytosis, silvery in psoriasis, greasy in seborrheic dermatitis, and crusted in pemphigus foliaceus. • Presence of facial edema • Purpura in dependent areas • Patients with drug eruption–related erythroderma may demonstrate evidence of leukonychia. • Hepatomegaly • Absence of evidence of the other disease, e.g. psoriatic plaques, flexural lichenification of atopics.
Laboratory	Suggestive findings include mild anemia, leukocytosis, eosinophilia, elevated erythrocyte sedimentation rate, and hypoalbuminemia.
Histopathological	Nonspecific in most patients. May show hyperkeratosis, parakeratosis, acanthosis, and a chronic perivascular inflammatory infiltrate, with or without eosinophils.
Evolution	Promptly clears within 2–6 weeks after withdrawal of the drug.
Provocation testing	Development of exfoliative dermatitis again after rechallenge test and improvement after stopping it leading to the diagnosis of drug-induced exfoliative dermatitis.

The treatment includes the following:

- Withdrawal of the suspected drug along with close monitoring
- In the acute phase of exfoliative dermatitis, treatment consists of measures to soothe the inflamed skin. These measures include bed rest, lukewarm soaks or baths, bland emollients to reduce insensible fluid losses, and enhance skin barrier function.
- Sedative oral antihistamines for pruritus
- Maintain temperature control for correction of hyperthermia or hypothermia.
- Balance of fluids and electrolytes should be closely monitored. Administered intravenous fluids to correct dehydration and correct electrolyte imbalance.
- A close vigil for possible secondary infection, whether cutaneous, pulmonary, or systemic should be kept.
- Antibiotic administration if secondary skin and soft-tissue infection is present.
- If reaction is severe, systemic steroid administration is required.

If the cutaneous reaction is not serious, desensitization can be attempted; but in case of serious reactions, reinstitution of drug is not to be attempted.

LEARNING ESSENTIALS

- ➢ Drug-induced, PR-like psoriasiform or erythroderma-like eruption should be actively looked for in cases where the rash is typical but persistent, severe, symptomatic, or where it is atypical.
- ➢ Diagnosis is based on detailed history and looking for clinical and laboratory clues to differentiate it from idiopathic forms of these diseases.
- ➢ Withdrawal of the offending drug brings speedy recovery and spares patient of prolonged suffering.
- ➢ Provocation testing can sometimes be helpful if undertaken in appropriate settings, if the definitive causal relationship cannot be established.

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Chapter

17

Phototoxic and Photoallergic Drug Reactions

Deepika Pandhi

SUMMARY

- Drug-induced photosensitivity is a cutaneous reaction due to exposure of the skin to a topically applied or systemically ingested drug that undergoes activation by ultraviolet light.
- The actual incidence of drug-induced photosensitivity is likely to be higher than the estimated 8% incidence in patients of adverse drug reaction as they are commonly misdiagnosed as contact dermatitis or as idiopathic or immunologic photodermatoses.
- Photosensitive drug reactions may be categorized as phototoxic or photoallergic in nature. Less common presentations include lichenoid, lupus erythematosus, pseudoporphyria, blue-gray pigmentation, pellagra reaction, and photoonycholysis.
- Photoallergy is an immune-mediated, type IV hypersensitivity reaction that presents with eczematous lesions predominantly over the sun-exposed sites, whereas phototoxic reactions result from a direct, toxic effect of the photolabile drug and mimic severe sunburn.
- A vast array of drugs are known to induce photosensitive skin reactions; however, the commonly reported photosensitizing agents include nonsteroidal anti-inflammatory drugs, antimicrobials, antimalarials, voriconazole, amiodarone, chlorpromazine, thiazides, and psoralens.
- Generally, the physical examination and a patient's history of development of photosensitive reactions following drug intake are of great importance for suspecting the diagnosis. The other contributory investigations include histology, phototesting, photopatch testing, and tests for exclusion of other photodermatoses.
- Drug withdrawal, sun avoidance, and protection by appropriate clothing and sunscreen are indicated, and treatment usually comprises of topical corticosteroids and oral antihistamines.

INTRODUCTION

Drug-induced photosensitivity is an undesirable sequel of topically or systemically administered drugs following exposure to sunlight. Drugs on photoactivation may induce development of cutaneous disease by two main mechanisms: photoallergy and phototoxicity. Although in many instances, it may be a challenge to distinguish between the two and indeed coexistence has also been reported, the differentiating characteristics are listed in Table 17.1. The other known mechanisms include—lichenoid, lupus erythematosus, pseudoporphyria, pellagra reaction, and photoonycholysis.[1,2]

EPIDEMIOLOGY

The prevalence of photosensitivity and photosensitive drug reactions in the general population is unknown.[3] It has also been stated that the majority of photosensitive drug reactions are undocumented and therefore may be under reported. Drug-induced photosensitivity comprised 7% of all photosensitive patients in a Scottish study reviewing data from 1970 to 2000.[4] Further, phototoxic drug reactions were diagnosed in 89% of these. The other presentations included photoallergic, lichenoid, lupus erythematosus, and pseudoporphyria. As usage of topical and systemic drugs may vary in different populations there is need for generating country-specific data for the prevalence

Table 17.1: Differentiation of photoallergic and phototoxic drug reaction

S. No	Variable	Photoallergic reactions	Phototoxic reactions
1.	Incidence	Less common	More common
2.	Amount of drug required/ UV dose	Low	High
3.	Mechanism	Immunologic response (type IV) to UV-altered drug in a sensitized individual	UV-activated drug causes reaction generating reactive oxygen radicals and cell damage in a nonsensitized host
4.	Onset	Delayed (24–72 hours)	Immediate (minutes to hours)
5.	Incidence after first exposure	No	Yes may occur
6.	Clinical Presentation	Mimics eczema. May involve nonphotoexposed skin.	Mimics sunburn with blistering, desquamation, and hyperpigmentation. Sharp delimitation may occur
7.	Distribution	Not restricted to areas of sun exposure	Restricted to areas of sun exposure
8.	Response to drug withdrawal	May recur after sun exposure	Reaction clears
9.	Cross-reactivity	Present	Absent
10.	Histopathology	Epidermal spongiosis with dermal infiltrate	Epidermal necrosis, dermal edema
11.	Diagnosis	Clinical and photopatch	Clinical and phototesting

of photosensitive drug reactions.[4] Photosensitive drug reactions are more common in adults as compared to children probably due to higher drug intake in the older age group.

PATHOGENESIS

Phototoxicity

Phototoxic reactions are nonimmunologic and primarily occur with drugs that are able to absorb radiation.[1] The biologic response may be seen with ultraviolet A (UVA) or UVB and is typically observed to occur above 310 nm. The absorption of UV radiation results in excitation of electrons and leads to the formation of singlet and triplet states of the photodynamic drug. These then transfer energy to oxygen and produce singlet oxygen species or generate free radicals that lead to lipid and protein denaturation and DNA damage.[3,5–7] This activity/activities are demonstrated by drugs like nonsteroidal anti-inflammatory drugs (NSAIDs), hydrochlorothiazide, furosemide, and chlorpromazine.[6] Fluoroquinolones have been reported to directly induce DNA breaks and lead to apoptosis, with keratinocytes being more vulnerable as compared to melanocytes.[7] Additionally, some photosensitizer drugs such as phenothiazines, chlorpromazine, tetracyclines, and quinolones may form stable photoproducts that act as photosensitizers.[3] In vivo, UVA is primarily incriminated versus UVB and visible light because of its deeper penetration[8] However, in vitro both UVA and UVB wavelengths are absorbed by the phototoxic compound. This phenomenon remains unexplained and it may be prudent to protect against both wavelengths.[6] Further, porphyrins and fluorescein react with visible light.[9] In another proposed mechanism, a photosensitizer drug may bind to its biological substrate with the help of radiation. Thereafter, an excited state molecule bonds covalently to a ground state molecule. This is best exemplified by 8-methoxypsoralen that bonds to the pyrimidine bases of DNA molecules forming DNA strands cross-links.[9]

The list of drugs causing phototoxic reaction is presented in Table 17.2.

Photoallergic Reactions

Photoallergic drug reaction is a cell-mediated immune reaction elicited by systemic but more commonly topical drugs in a sensitized host. The photoactive compound serves as a hapten and a larger carrier protein molecule transforms it into a complete antigen. Photoallergy is induced by halogenated salicylanilides, chlorpromazine, and para-aminobenzoic acid by means of this mechanism.[9] The drugs inducing photoallergic reaction are presented in Table 17.3. The subsequent cascade is similar to allergic contact dermatitis; the antigen is presented by Langerhans cells in association with major histocompatibility complex (MHC) class II to T lymphocytes in lymph nodes. These activated T cells home into the sun-

Table 17.2: Medications causing phototoxicity

Group of drugs	Medication
Topical	
1. Antibiotic	Cotrimoxazole Erythromycin
2. Anti-inflammatory/ Anesthetic	Benzocaine Diclofenac Ketoprofen
3. Miscellaneous	Halogenated salicylanilides Benzoyl peroxide Benzophenone Cinnamate Coal tar Fluorescein Ketoconazole Para aminobenzoic acid Porphyrins Psoralens Tretinoin
Systemic	
1. Antibiotic	Tetracyclines Fluoroquinolone Sulfonamides Dapsone
2. Anti-inflammatory/ anesthetic	Ibuprofen Ketoprofen Naproxen Celecoxib Nalidixic acid Piroxicam
3. Antifungal	Griseofulvin Ketoconazole Voriconazole Itraconazole
4. Hypoglycemic	Glibenclamide
5. Cardiovascular and diuretics	Diltiazem Enalapril Furosemide Quinidine Thiazides Nifedipine
6. Miscellaneous	Chloroquine Azathioprine Erlotinib Etretinate Isotretinoin Leflunomide Oral contraceptive Phenothiazines Porphyrins Psoralens Vemurafenib

Table 17.3: Medications capable of inducing photoallergy

Group of drugs	Medication
Topical	
1. NSAIDs/anesthetics	Naproxen Dibucaine Diclofenac Etofenamate Flufenamic acid Piroxicam Tiaprofenic acid Ketoprofen
2. Miscellaneous	Acyclovir Chloramphenicol Benzophenone Epoxy resin and devices 5-Fluorouracil Hydrocortisone Furocoumarins Halogenated salicylanilides
Systemic	
1. Antibiotics	Dapsone Sulfonamide Moxifloxacin Minocycline Tetracycline
2. Antifungal	Itraconazole Ketoconazole Voriconazole
3. Anti-inflammatory	Piroxicam Ketoprofen Celecoxib Ibuprofen Nalidixic acid Paracetamol
4. Antineoplastic	Hydroxyurea Imatinib 5-Fluorouracil Capecitabine Vemurafenib Vinblastin Paclitaxel
5. Cardiovascular and diuretics	Quinidine Thiazides Amiodarone Nifedipine Methyldopa Verapamil Ramipril
6. Hypoglycemics	Sulfonylureas Sitagliptin
7. Neuroleptics	Phenothiazines– Carbamazepine Phenytoin
8. HMG-CoA reductase inhibitors	Statins
9. Miscellaneous	Chloroquine Citalopram Clofibrate Clopidogrel Eculizumab Efavirenz Flutamide Leflunomide Para aminobenzoic acid Ranitidine Venlafaxine Cinnamates

exposed sites and on photoexposure initiate an inflammatory response.[1,2,8] The longer UVA wavelengths are usually incriminated. The presentation may vary depending on whether the photoallergy is secondary to a topical agent (which elicits an eczematous response) or a systemic agent-induced reaction (which elicits an exanthematous eruption). The factors influencing outcome include drug dosage, radiation quantity and spectrum, Fitzpatrick skin type, and thickness of horny layer.[8,10]

CLINICAL FEATURES

Phototoxic Drug Reactions

Phototoxic reactions occur at any age, predominantly in women.[1] A phototoxic reaction occurs within minutes to hours of sun exposure. The initial complaint is burning and stinging and within 24 hours this is followed by development of erythema and edema over the exposed areas such as face, ears, V area of the neck, extensors of forearms and hands mimicking sunburn (Figs. 17.1 and 17.2). Post auricular areas, submental areas,nasolabial folds and skin protected by clothing are spared due to lack of exposure to UV radiation (Figs. 17.3 and 17.4). [2,8,9] In severe cases, vesiculation, bulla formation, and desquamation may occur. Indeed toxic epidermal necrolysis triggered by sun exposure in a patient on long-term hydroxychloroquine has been reported.[11] Healing occurs with hyperpigmentation.[2,8,10] Drug-specific sequelae may be evident, for example, brown

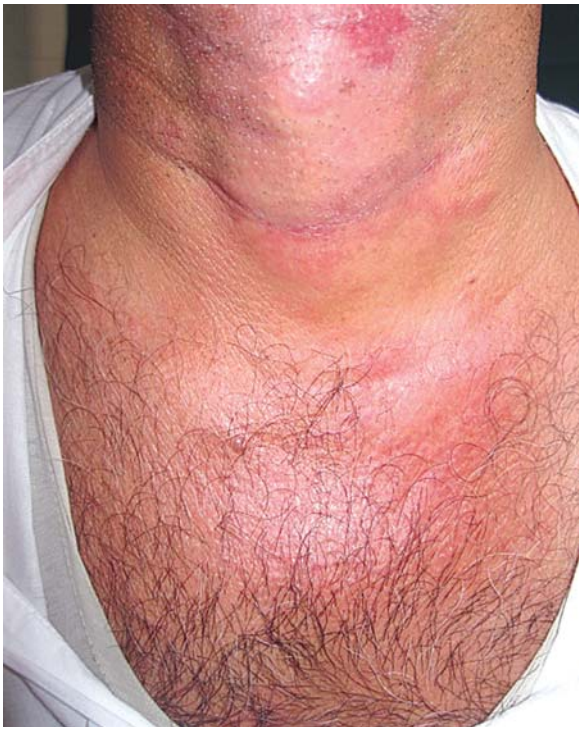

Fig. 17.1: Severe phototoxic reaction with erosions induced by furosemide.

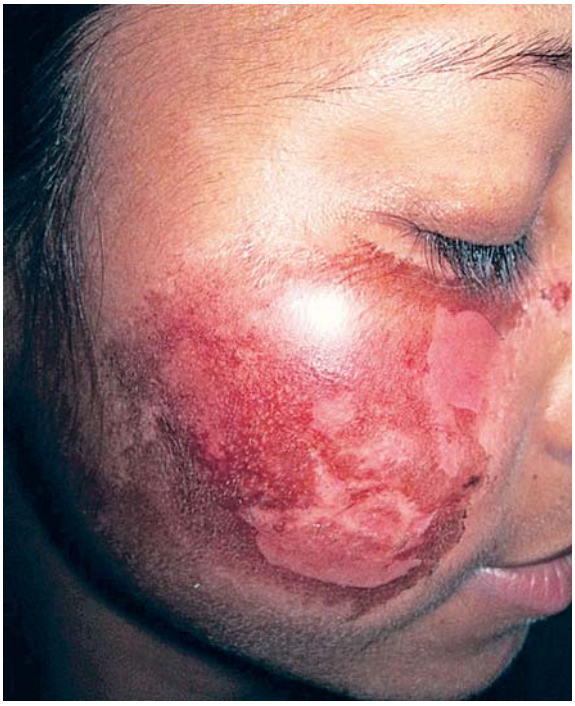

Fig. 17.2: Localized phototoxic reaction to topical retinoids in a patient of acne vulgaris.

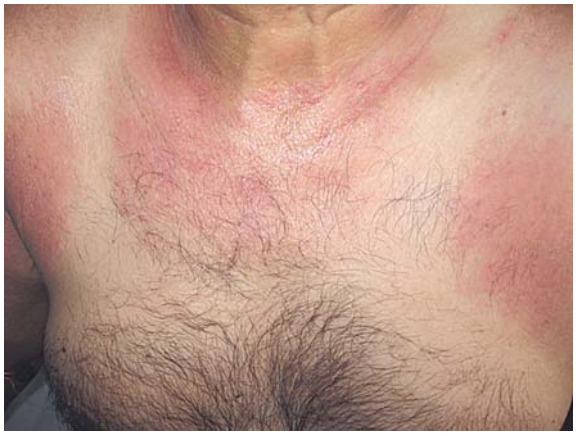

Fig. 17.3: Phototoxic reaction to Glibenclamide in a male diabetic patient. Note strict demarcation to areas exposed by vest.

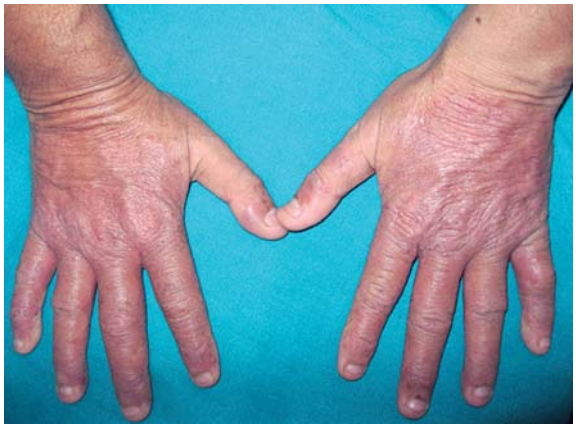

Fig. 17.4: Involvement of dorsa of hand in same patient as in Fig. 17.3.

pigmentation with psoralens.[10] In cases with persistent exposure, chronic actinic dermatitis may develop presenting with pruritic lichenified lesions showing secondary excoriation over the sun-exposed regions. This type of reaction is more likely with thiazides, quinidine, amiodarone, and quinine. Further, in patients who have received long-term psoralen and ultraviolet A (PUVA) photochemotherapy, cutaneous sequelae are seen in the form of premature aging of the skin, thickening of the skin, giant lentigines, squamous cell carcinoma, and melanoma.[12]

Photoallergic Drug Reaction

Photoallergic dermatitis occurs in patients of any age but men are affected more commonly than women.[1] The most common cause of photoallergic reactions in United States and Europe are sunscreen products including UV filters like benzophenone-3.[13] The other commonly reported causes include antimicrobial agents and NSAIDs.[9] The common medications responsible for this kind of reaction are detailed in Table 17.3. The initial complaint is pruritus. Subsequently, in 24–72 hours, acute eczematous lesions with erythema, edema, and vesiculation develop in the sun-exposed sites—face, neck and dorsa of hands but lesions may spread to covered sites as well (Figs. 17.5 and 17.6).[2] In chronic exposure, the reaction becomes persistent with lichenification and a rash resembling chronic actinic dermatitis. Interestingly, a predilection for skin with preexisting dermatitis has been described.[2] Hyperpigmentation usually is not a sequel of photoallergic drug reactions. Subsequent exposure to the inciting drug or a cross-reactive compound and the sun may cause a faster drug reaction (24–48 hours).[8] Long-term intake of chlorpromazine, dioxopromethazine, ketoprofen, halogenated salicylanilides, and quinidine, with chronic UV radiation, may also cause chronic actinic dermatitis, as in phototoxic reactions.[9]

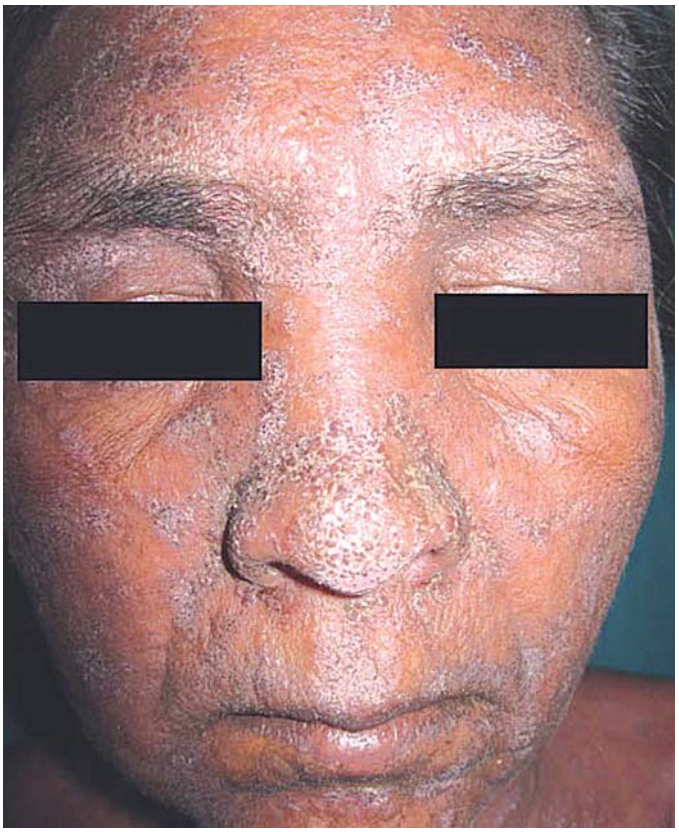

Fig. 17.5: Photoallergic dermatitis in a patient on carbamazepine.

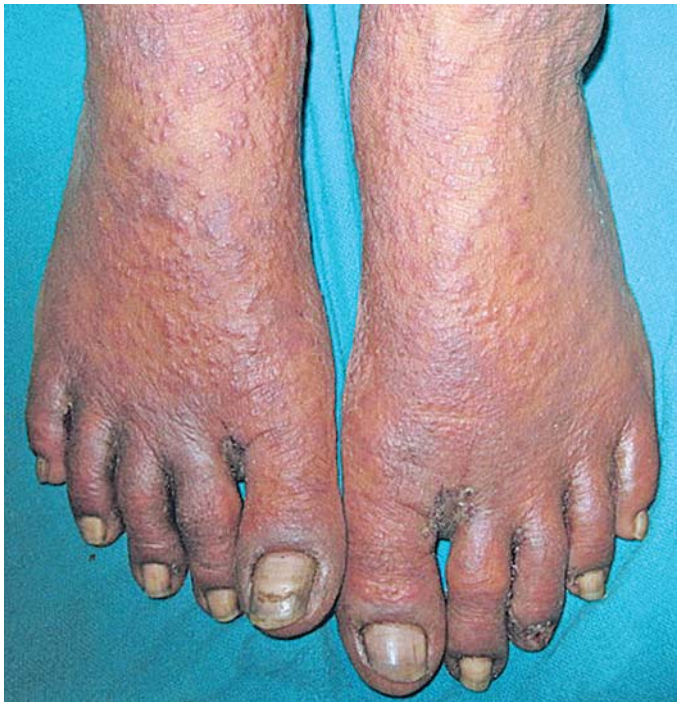

Fig. 17.6: Involvement of dorsa of feet in same patient as in Fig. 17.5.

Lichenoid photosensitive reactions present as violaceous flat-topped pruritic papules and plaques in photo-exposed distribution (Figs. 17.7 and 17.8). The most commonly incriminated drugs include thiazide diuretics, NSAIDs, phenothiazines, quinidine, capecitabine, imatinib, and clopidogrel.[2]

Photoonycholysis is a painful separation of the distal nail plate from the nail bed that occurs by exposure to the drug and UV energy. This represents systemic drug–induced toxicity and the absence of melanin increases the susceptibility of this site to phototoxicity.[2,9] The classification is based on the degree of distal nail plate separation from nail bed as is described in Box 17.1.[14] The drugs most likely to induce photoonycholysis are tetracyclines and doxycycline and they have been shown to produce a dose-dependent response. The other drugs include quinine, olanzapine, paclitaxel, carbamazepine, and psoralens.[2,4]

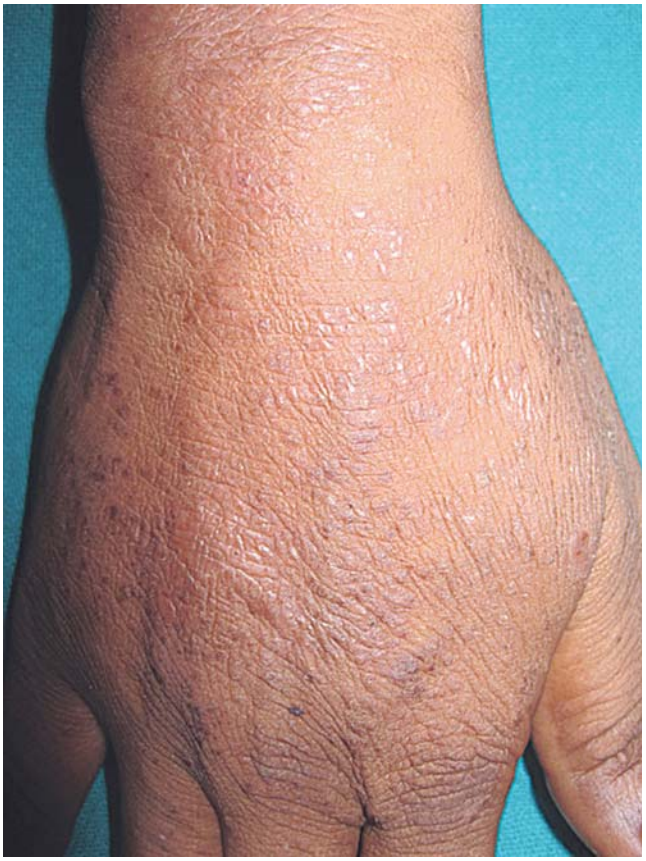

Fig. 17.7: Lichenoid papules over dorsum of hand induced by carbamazepine.

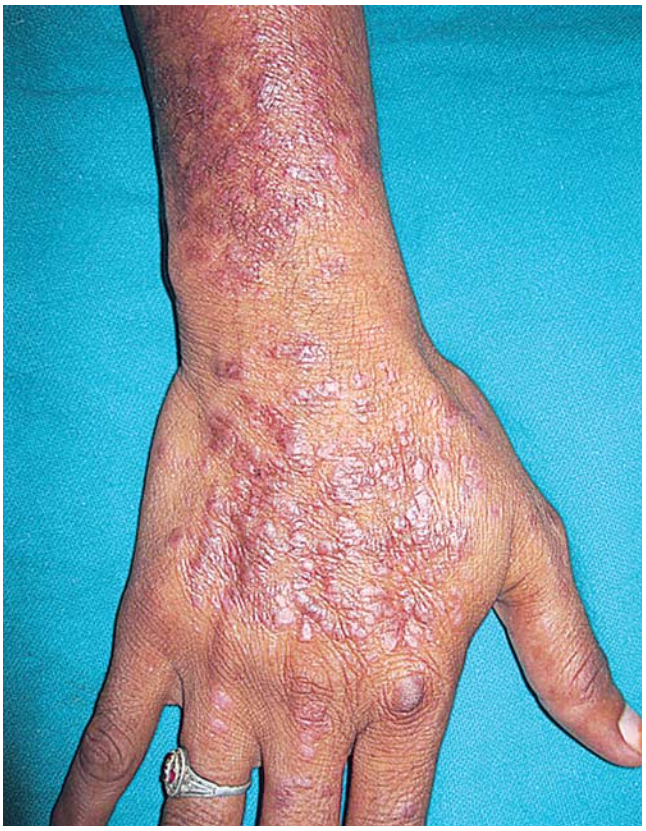

Fig. 17.8: Lichenoid photosensitive reaction caused by thiazide.

Box 17.1: Types of photoonycholysis[14]
Type I: Concave distal separation
Type II: Convex distal separation with notched opening
Type III: Central nail plate changes

Pseudoporphyria appears commonly in patients of chronic renal failure on photoactive medications. The primary target is at the dermoepidermal junction and patients present with photosensitivity, easy bruising, vesiculation and subepidermal bullae formation over the sun-exposed sites.[2,4] The cutaneous, histologic, and immunofluorescence findings in this phenomenon are identical to those seen in porphyria cutanea tarda. The diagnosis is made clinically by eliciting history of sun exposure and drug intake, and most importantly by estimation of normal porphyrin levels.[9] These cutaneous changes are reversible on drug withdrawal. This presentation is most commonly attributed to the following drugs—naproxen, furosemide, tetracycline, nalidixic acid, fluoroquinolones, sulfonamides, beta-lactam antibiotics, nifedipine, chlorpromazine, retinoids, piroxicam, amiodarone, cyclosporine, imatinib, oral contraceptives, quinidine, and voriconazole.[2,4,9] In the case of voriconazole, especially in immune-compromised patients and with drug intake of more than 12 weeks, accelerated phototoxic changes may be seen. The presentation may include pseudoporphyria, photoaging, lentigines, premature dermatoheliosis, squamous cell carcinoma and melanoma. Malignancy has been reported even after 12 months of drug intake.[12]

Phototoxicity due to some drugs may present as *blue-gray pigmentation* predominantly in sun-exposed areas.[15] Amiodarone, minocycline, chlorpromazine, clozapine, and imipramine may induce this reaction. Minocycline may cause blue-gray pigmentation over the face with a predilection for acne scars and minor involvement of shins and forearms. Argyria presents with a *slate-gray pigmentation* that also involves the nail lunula, mucous membranes, and sclera. This is induced by the dermal deposition of silver granules that have been produced during a photochemical reaction.[9,15]

Telangiectasias—Nifedipine and its congeners have been reported to produce telangiectasias predominantly over the face. These may be associated with photodamaged facial skin thereby suggesting development of phototoxicity. These resolve on drug cessation and recur on reinitiating nifedipine. Other drugs reported to cause this presentation are venlafaxine and cefotaxime.[2,4]

Differential Diagnoses

The differential diagnoses comprise other photodermatoses that are skin disorders caused or aggravated by UV radiation and /or visible light. These have been classified into four groups: (i) immunologically mediated photodermatoses (idiopathic), (ii) chemical-induced photosensitivity, (iii) defective DNA repair disorders, and (iv) photoaggravated dermatoses (Table 17.4).[16]

Table 17.4: Classification of photodermatoses

Mechanism of photosensitivity	Presentation
1. Immunologically mediated photodermatoses (idiopathic)	• Polymorphous light eruption • Solar urticaria • Actinic prurigo • Hydroa vacciniforme • Chronic actinic dermatitis
2. Drug- and chemical-induced photosensitivity	• Phototoxic • Photoallergic • Pseudoporphyria • Lichenoid • Blue-gray pigmentation • Photoonycholysis • Lupus erythematosus
3. Defective DNA repair disorders;	• Xeroderma pigmentosum • Cockayne syndrome • Bloom syndrome • Rothmund–Thomson syndrome • Trichothiodystrophy • Kindler syndrome
4. Photoaggravated dermatoses	• Lupus erythematosus • Rosacea • Lichen planus • Darier's disease • Atopic eczema • Herpes simplex • Pellagra • Pemphigus foliaceus or erythematosus

Clinical features of photodermatoses are diverse and they are suspected if the skin eruption predominantly appears in the UV-exposed areas. A careful history and examination and appropriate investigations (Box 17.2) may help in establishing a diagnosis of drug-induced photosensitive reaction.

Allergic contact dermatitis caused by inhaled allergens may mimic photoallergic reactions. However, it predominantly affects the skin folds like nasolabial folds and eyelids; areas that are usually exposed to minimal UV irradiation; and thus, are not expected to be involved in photo-induced reactions.[9]

APPROACH TO DIAGNOSIS

The approach to diagnosis of photosensitivity and in determining if a drug is causative is listed in Box 17.2.

Box 17.2: Approach to diagnosis

- Detailed history including: drug intake, dosage, sun exposure with quantum, temporal relation of cutaneous lesions with drug intake, use of other photosensitizers, systemic complaints, seasonal variation, occupational history, and family history.
- Physical examination—for ascertaining distribution of lesions: sun-exposed/protected areas, morphology: erythema, urticaria, edema, papules, vesicles, blisters, eczema, telangiectasias.
- Histopathology

  Phototoxic—Spongiosis, necrotic, keratinocytes, dermal edema.

  Photoallergic—Epidermal spongiosis with dermal infiltrate.
- Patch testing and photopatch testing
- Rechallenge

  Phototesting—exposure to UVA, UVB, and visible light

  Take immediate reading and MED determination after 24 hours.

  Provocation testing for abnormal responses (four to five times at the same site)
- Laboratory investigation

  Full blood count (eosinophilia)

  Liver function tests

  Serum antinuclear antibody (ANA),

  anti-double stranded DNA (dsDNA),

  anti-Ro/La, porphyrin profile.

Histopathology

In phototoxic reactions, epidermal spongiosis, necrotic keratinocytes, and in severe cases, epidermal necrosis are evident. In the dermis, edema, and mild inflammatory infiltrate of neutrophils, lymphocytes, and macrophages are observed. In lichenoid eruption, the findings are similar to those of lichen planus except for more marked spongiosis, dermal eosinophils, plasma cell infiltrate, and an increased number of necrotic keratinocytes and cytoid bodies. In the case of slate-gray pigmentation, increased dermal melanin and dermal deposits of the drug are found. In pseudoporphyria, a dermal–epidermal cleft is present at the lamina lucida level akin to porphyria cutanea tarda and immunoglobulin deposits are seen at the dermoepidermal junction and around the dermal blood vessels.[2,9]

Histopathologic findings in photoallergy are similar to those of allergic contact dermatitis with evidence of epidermal spongiosis with dermal mononuclear cell infiltrate.[2,9]

Photopatch Testing

Photopatch testing may be useful in evaluating photosensitivity to topical medications presenting as a photoallergic response. Photopatch testing is not recommended in cases of suspected phototoxicity. Photopatch tests may be negative in photoallergy with medications delivered by enteral or parenteral routes, because a specific metabolite is inducing the cutaneous lesions.

Photopatch testing is similar to standard patch testing and should not be performed while the dermatitis is active. It should be undertaken on uninvolved skin that has not been active for the previous 2 weeks to avoid the "angry back" syndrome. The best site for the photopatch testing is the skin of the upper back, avoiding the paravertebral area. Photopatch tests are done in duplicate because photosensitizers may also elicit contact hypersensitivity. One set is removed after 24 hours and irradiated with UVA of 5–10 J/cm^2. After 48 and 72 hours, both sets of patch tests (the irradiated and nonirradiated sides) are evaluated for a positive reaction (manifested as erythema, edema, and/or vesicles after 48 hours). A similar positive reaction at both sites is interpreted as an allergic contact dermatitis; the positive response at an irradiated site and negative at nonirradiated site is interpreted as a positive photopatch test reaction (Table 17.5).[1,5,8]

Table 17.5: Interpretation of photopatch test

Reaction at non-irradiated site	Reaction at irradiated site	Interpretation
Negative	Negative	No reaction
Negative	Positive	Photoallergic reaction
Positive	Positive	Contact reaction
Positive	Strongly positive	Photoaggravated reaction

Phototesting

Phototesting with UVA, UVB, and in some instances, visible light is helpful in diagnosing photosensitivity disorders. This test is performed while patient is on suspected drug, by exposing small areas of skin on the back or inner aspect of the forearms to elicit the minimum erythema dose. Minimum erythema dose (MED) is the minimum dose of light required to produce uniform erythema over the entire irradiated site at 24 hours. Patients with phototoxic reactions generally have a reduced MED to UVA and/or to UVB and on subsequent testing, after drug elimination, an increase in the UVA MED is observed.[1,5,8] Akin to photopatch testing, systemic immunosuppressants and topical agents should be discontinued 2 weeks before testing.[9]

Photosensitizing Drug Potential

The importance of evaluating the potential risk of all new drugs in causing a photosensitive reaction and knowledge of the drug's potential in inducing photosensitive adverse reaction is crucial before instituting any treatment modality. Till date, no single ideal method for evaluating drug photosensitivity potential has been established. A panel of in vitro and in vivo assay systems have been used for the assessment of or confirmation of the photosensitizing potential of a new compound. In vitro methods used for initial screening for photosensitivity include measurement of UV and visible light absorption spectra of the drug; quantification of the ability to photo-oxidize histidine, to induce photohemolysis, to inhibit yeast growth, mitogen-induced lymphocytic blast transformation, and ability to bind to a protein carrier such as serum albumin. Experimentally, human skin response to drugs and UV exposure has been reproduced in hairless mice, guinea pigs, albino mice, and retinal tissue.[9,17]

MANAGEMENT

Successful management of a photosensitive drug reaction often presents a challenge for the dermatologist. The most vital component is an intensive counseling providing detailed information about provoking drugs, role of UV light and sun exposure, and what preventive measures are required. These could entail a change of occupation and avoidance of midday sun, use of protective plastic films over windows, and windscreens. Photoprotection is the mainstay of treatment and it is recommended to wear closely weaved clothing that covers most of the body and regular use of umbrella may be advised. It is extremely important to recommend an adequate sunscreen that provides UVA protection in addition to UVB and visible light as UVA radiation has primarily been incriminated in the causation of both phototoxic and photoallergic drug reaction. Sunscreens that contain avobenzone, titanium dioxide, and zinc oxide are more effective in blocking out UVA radiation.[16,18,19]

Once a diagnosis of a drug-induced photosensitive drug reaction is confirmed and the offending drug identified, discontinuation of the suspected topical or systemic drugs should be recommended and

alternative drugs prescribed ensuring lack of cross-reactivity. Although persistent photosensitivity may occur especially in photoallergic dermatitis, in most cases the photosensitivity and reaction subsides after the photosensitizing medication withdrawal. In symptomatic patients, antihistamines are generally helpful in minimizing the itching and high-potency topical corticosteroids are warranted. Short-term systemic steroids (prednisone 1 mg/kg) for 1–2 weeks can be initiated for acute and severe reactions.[8,9,17] It has been observed that in patients with sparfloxacin-induced photosensitivity, delayed treatment made the reaction more difficult to treat and an early treatment of the reaction is advisable.[18]

Symptomatic therapy alone is adequate for patients with slate-gray pigmentation, lichenoid eruption, pseudoporphyria, and photodistributed telangiectasia. However, the evident response may be slower and it can take a few months for the reaction to subside. Persistent marked hyperpigmentation may cause psychological distress and depigmentation therapy. Kligman's formulation, or laser therapy can be attempted.[9,20] A patient with amiodarone-induced photosensitivity has been treated with gradually increasing doses of narrowband UVB phototherapy in an attempt to induce improved sun tolerance. This patient was sensitive to UVA and visible radiation and the narrowband UVB phototherapy increased the symptom-free time outdoors patient from <30 minutes to 3–4 hours.[21]

Reactive oxygen species have mainly been stated to incite phototoxicity; therefore, antioxidant supplements may be useful adjuncts in treatment.[6] The line of management is summarized in Box 17.3.

Box 17.3: Management of patients with photosensitive drug reaction

- Identification and drug withdrawal
- Photoprotection
  - Physical
  - Sunscreen—UVA + UVB + physical sunscreen
- Symptomatic treatment
- Topical corticosteroids
- Oral corticosteroids
- Photoprophylaxis
- Antioxidants
- Counseling

LEARNING ESSENTIALS

- In the past few decades, drug-induced photosensitivity of the skin is drawing increasing attention and is now considered as a cause of concern by the clinicians, drug controllers, and the pharmaceutical industry.
- It has been recommended that all potential drugs should be screened for photosensitizing potential before they are released for clinical trials.
- The photosensitivity is primarily of two types: phototoxicity and photoallergy. Phototoxic disorders have a higher incidence as compared to photoallergic reactions.
- It is imperative to always consider drug-induced photosensitivity when a patient presents with a skin eruption and a history of medication use combined with UV exposure is elicited.
- The action spectrum for photosensitivity reactions is mostly within the UVA (320–400 nm) and visible light range, and rarely in UVB (290–320 nm) range.
- A wide array of drugs may induce phototoxic and photoallergic reactions.
- Drug-induced photosensitivity may present a diagnostic difficulty, especially with systemic medications.
- There have been advances made in the development of testing tools: currently available testing methods include phototesting, photopatch, photoprick, and several in vitro tests. If the photosensitizer is not the drug but a metabolite of the drug substance, a systemic photoprovocation test may be employed.

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Chapter

18

Bullous Drug Reactions

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SUMMARY

Drug-induced bullous disorders include pemphigus, bullous pemphigoid, linear IgA bullous dermatosis, and pseudoporphyria. A wide variety of drugs can induce these disorders and the list is ever-increasing. These disorders are rare and often the association with drug intake is based on an anecdotal report. Drug-induced bullous dermatoses are often indistinguishable from the idiopathic disease. Clinical features are usually similar to the classical disease and high index of suspicion is required for diagnosis. Recent introduction of a new drug in the patient's therapeutic regimen, resolution of the symptoms on withdrawal of the drug, and no recurrence thereafter are the pointers to the diagnosis. Rechallenge is not recommended as the diseases may be severe in nature. Withdrawal of the drug is the first step in management. During the acute episode, the patients may be treated as in classical disease but adjuvant immunosuppressive therapy is not required.

INTRODUCTION

Drug-induced bullous disorders are unique as these do not come under the purview of classical adverse drug reactions despite drugs being involved in the causation. In general, the term "drug induced" has been used when there is rapid resolution of the dermatoses following withdrawal of the drug.[1] When there is onset of the dermatoses with drug intake but it persists even after withdrawal of the drug, the term "drug triggered" is used.[1]

Various drug-induced bullous disorders have been presented in Box 18.1. Of these, pemphigus, bullous pemphigoid (BP), and linear IgA bullous dermatosis (LABD) are immunobullous disorders. The other is drug-induced pseudoporphyria. Table 18.1 lists the drugs causing these disorders.[1–10] However, this list is nonexhaustive; with invention of newer pharmacological agents, there are reports of newer drugs causing these disorders. Clinical features of these dermatoses are usually indistinguishable from those of classical ones. However, there are subtle points of difference and high index of suspicion is necessary in the context of using the drugs known to cause these dermatoses. As these disorders are rare, pathogenesis is poorly understood. The possible pathomechanism, clinical features, management, and prognosis of drug-induced bullous disorders have been discussed individually in the following section.

Box 18.1: Various drug-induced bullous disorders

- Drug-induced pemphigus
- Drug-induced bullous pemphigoid
- Drug-induced linear IgA disease
- Pseudoporphyria

DRUG-INDUCED PEMPHIGUS

Pathomechanism

There are four groups of drugs causing pemphigus: "thiol drugs", "amide drugs", "phenolic drugs", and "non-thiol, non-phenol drugs".[1] In a series of 17 Japanese patients with drug-induced pemphigus, thiol-containing drugs were the commonest causative agent.[11] Drugs can induce acantholysis solely by biochemical mechanism or in combination with immune mechanism. In the former, drugs directly interfere with the keratinocyte architecture. In the latter, drugs induce autoantibody production to cause acantholysis.[1]

Table 18.1: Various drugs inducing bullous disorders[1–10]

Disorder	Drugs
Pemphigus	Common: D-penicillamine, captopril, penicillin
	Uncommon: Rifampin, pyritinol, thiopronine
	Rare: Cephalosporins, gold salts, methimazole, L-dopa, opioids, phenobarbitone, phenytoin, IL-2, α-interferon, piroxicam, phenylbutazone, aspirin, nifedipine, propranolol, angiotensin-converting enzyme inhibitors (ACEIs) other than captopril, vaccines, amoxicillin-clavulanic acid, isotretinoin, isoniazide, ethambutol, imiquimod, progesterone, infliximab[3], etanercept[4]
Bullous pemphigoid	Common: Furosemide, sulfasalazine
	Uncommon: Penicillin, spironolactone, aspirin
	Rare: Galantamine hydrochloride (anticholinergic), fluoxetine, risperidone, levofloxacin, cefalexin, ampicillin, sulfapyridine, ibuprofen, D-penicillamine, bumetanide, enalapril, captopril, IL-2, sulfonamides, omeprazole, amiodarone, terbinafine, chloroquine, phenacetin, oral hypoglycemic agents, rosuvastatin[5], intravenous iodinated radiocontrast media[6], dipeptidyl 4-peptidase inhibitors (vildagliptin, sitagliptin)[7]
Linear IgA disease	Common: Vancomycin
	Uncommon: Captopril, co-trimoxazole
	Rare: Phenytoin, cefamandole, ceftriaxone, penicillin, piroxicam, naproxen, diclofenac, amiodarone, acetaminophen, somatostatin, lithium, rifampicin, atorvastatin, imipenem, furosemide, verapamil, ketoprofen, interleukin (IL)-2, interferon-γ
Porphyria cutanea tarda	Furosemide, torsemide, naproxen, tetracyclines, fluoroquinolones, voriconazole, chlorthalidone, butamide, hydrochlorothiazide, triamterene, amiodarone, cyclosporine, psoralen and ultraviolet A (PUVA), narrowband ultraviolet B (NB-UVB), diclofenac[8], naproxen, ketoprofen, mefenamic acid, aspirin, rofecoxib, ampicillin–sulbactam, cefepime, isotretinoin, acitretin, etretinate, erythropoietin, 5-fluorouracil, cyclosporine, dapsone, flutamide, OCP, pyridoxine, N-acetyl cysteine[9] nalidixic acid[10]

ACEIs - angiotensin converting enzyme inhibitors; OCP - oral contraceptive pill

Various mechanisms by which drugs may cause pemphigus have been presented in Table 18.2.[1,12] Thiol drugs contain a sulfhydryl (–SH) group in their structure. Thiol groups usually induce pemphigus foliaceus (PF), whereas non-thiol groups usually trigger pemphigus vulgaris (PV), which tend to persist even after withdrawal of the drug.[12] ACEIs contain active thiol as well as active amide groups in their structure. This makes this group of drugs more vulnerable to induce PV and PF.[12] It has been observed that more than 50% of hypertensive patients (without pemphigus) receiving ACEI may have circulating anti-desmoglein antibodies.[13] Some drugs (β-lactam antibiotics, spirapril) are categorized as "masked thiols"; there is a sulfur group in their structure with the potential to form –SH group during biotransformation and is responsible for drug-induced pemphigus.[1,12]

Table 18.2: Possible mechanisms of drug-induced pemphigus[1,12]

Group of drugs	Mechanisms
Thiol drugs	• Biochemical mechanism - Inhibit the keratinocyte transglutaminase enzyme responsible for aggregation of cells - Disturbed keratinocyte adhesion by forming thiol–cysteine bond in place of cysteine–cysteine bond - Activation of keratinocyte-disaggregating enzymes acetylcholine esterase by ACE inhibitors • Immune mechanism - Drugs/metabolites bind to proteins to form haptens, which modify T- and B-cell response toward loss of self-tolerance and modify keratinocytes to produce anti-desmosomal antibodies
Phenolic drugs	• Release of cytokines from keratinocytes; tumor necrosis factor (TNF)-α and IL1-α activate plasminogen activator, causing acantholysis
Non-thiol, Non-phenol drugs:	
Angiotensin II receptor blocker	• Autoantibody production by indirect immune mechanism rather than direct biochemical modification of the keratinocyte antigens
Calcium channel blockers	• May alter desmoglein turnover, as these are desmosomal cadherin-calcium dependent adhesive molecules

Genetic factors may also play a role in the development of drug-induced pemphigus, as neither everyone taking these drugs develop, nor all drugs with the same chemical structure induce these dermatoses.[12] Concurrent underlying factors such as malignancy may also be additive to the pathogenesis in elderly patients.[12] In many of the patients with idiopathic pemphigus, poor control of the disease despite adequate therapy may be related to the concomitant administration of drugs that induce pemphigus.[12] Considering all these factors, Pietkiewicz et al. have proposed the pathogenesis-based categories of drug-induced pemphigus as follows[12]:

- Activation of pemphigus autoimmunity by specific pemphigus-inducing drugs without clinical pemphigus.
- Manifested clinical pemphigus only by specific pemphigus-inducing drugs.
- Causation of clinical pemphigus by specific pemphigus-inducing drugs in presence of multiple other factors (multifactorial).
- Onset of clinical pemphigus by drugs not known to induce it and the disease course being modified by specific pemphigus-inducing drugs (concurrent drug administration).
- Idiopathic pemphigus, the course being modified by administration of specific pemphigus-inducing drugs.

Clinical Features

Skin lesions may appear any time by 6 months of initiation of the drug.[2,14] It may be longer for thiol group of drugs.[12] Drug-induced PF phenotype is common than PV.[12] The lesions are flaccid vesicles and bullae (Fig. 18.1)and often diffuse moist scaling and crusting are present (Figs. 18.2 A and B).[14] Oral involvement is usually absent. Rarely, pemphigus herpetiformis-like morphology may be present.[11]

Thiol drugs mostly induce PF and non-thiols PV.[11,12] Among the antihypertensive drugs, ACEIs and angiotensin-receptor blockers (ARBs) have been found to induce both PV and PF.[3] Methyldopa mostly induces PV.[12] Calcium channel blockers, thiazide diuretics, and β-blocker-thiazide diuretic combination have been found to induce PF.[12]

Investigations

Histopathology and direct immunofluorescence (DIF) study findings of drug-induced pemphigus are indistinguishable from the idiopathic one. Indirect immunofluorescence (IIF) study from the sera of these patients is usually negative. However, in some patients, IIF may detect circulating autoantibodies to desmogleins 1 and 3.[2,11] If IIF is negative, enzyme-linked immunosorbent assay (ELISA) and/or immunoblot assay may be performed to assess the presence or absence of these circulating autoantibodies.[11] In a series of 17 Japanese patients with drug-induced pemphigus, Yoshimura et al. have detected paraneoplastic pemphigus-like reactivity (envoplakin and periplakin) in addition to positivity with desmoglein 1, even in the absence of detectable malignancy.[11]

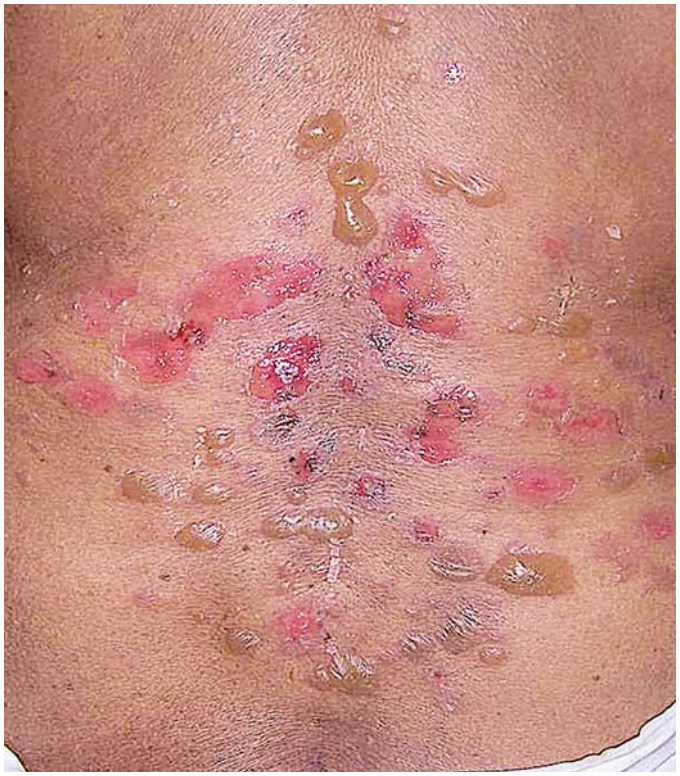

Fig. 18.1: Bullous drug reaction; flaccid pemphigus vulgaris like bullae in a patient on anti-tubercular treatment, Rifampicin was the suspected drug.

Immunostaining with monoclonal anti-32-2b antibody helps in differentiating idiopathic and drug-induced pemphigus.[15] A positive staining by this method indicates autoimmune pemphigus which persists even after withdrawal of the drug.

In vitro interferon-γ release assay (IGRA) may pinpoint the particular drug inducing pemphigus.[7] This may be helpful when a patient is on multiple drugs and obviates the need for rechallenge.

Prognosis

In 50% cases, drug-induced pemphigus resolves after withdrawal of the offending drug.[11] However, sometimes the disease persists or recurs after an interval even without readministration of the drug. Pemphigus vulgaris induced by non-thiol drugs tend to persist even after withdrawal.[7] Some patients may have an intractable disease course and may turn out to develop classical pemphigus.[7]

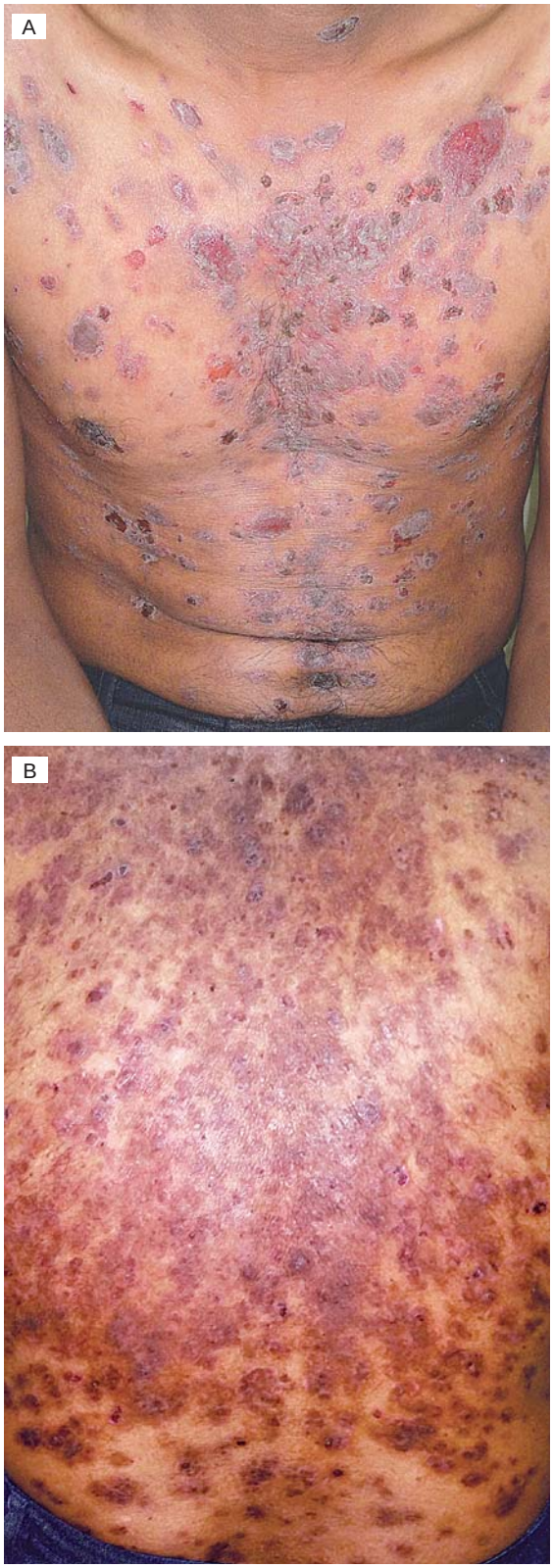

Fig. 18.2: (A) Pemphigus foliaceous like drug rash in a patient on captopril; (B) Pemphigus foliaceous due to Gold in a patient with rheumatoid arthritis.

Management

Withdrawal of the suspected drug is a must. Pemphigus is managed as per existing treatment protocol.

DRUG-INDUCED BP

Pathomechanism

The most common drug inducing BP is furosemide (Fig. 18.3).[16,17] Other commonly reported drugs are aldosterone antagonists[17], neuroleptics[17], ACEIs, and anticoagulants.[18] The causative drug may bind to lamina lucida causing unmasking of some hidden antigenic components and change their antigenic properties.[5] The basement membrane zone (BMZ) antigens against which autoantibodies are formed are probably same as in idiopathic BP i.e. BP230 and BP180. Various hypotheses regarding pathogenesis of drug-induced pemphigoid have been presented in Table 18.3.[7]

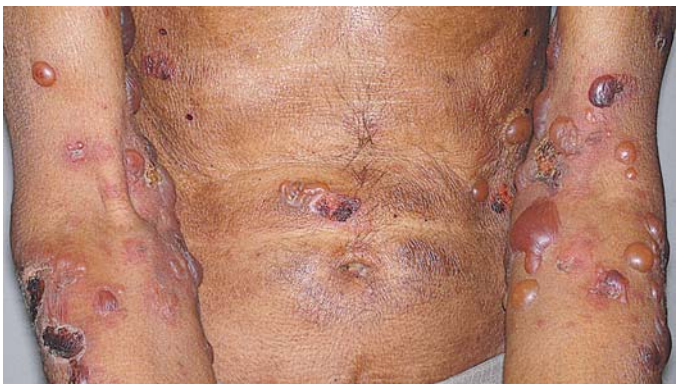

Fig. 18.3: Bullous pemphigoid in a patient on furosemide for hypertension.

TNF-α inhibitors have been used successfully in the treatment of BP concomitantly occurring in patients with psoriasis.[19,20] The basis for therapeutic effect of these agents in patients with BP is the high level of TNF-α demonstrable in the sera and blister fluid of patients with idiopathic BP.[7] Contradictory to the above, there are reports of patients with psoriasis and rheumatoid arthritis treated with various TNF-α inhibitors developing BP; etanercept,[6] adalimumab[3], and efalizumab[3] were the causative agents and the time of onset of the lesions varied from 6 weeks to 2–3 years after initiation of the treatment. How these therapeutic agents may cause such paradoxical effect is not clear. Dysregulation of TNF-α levels in the background of preexisting inflammatory diseases resulting in a true drug reaction or conversion of a subclinical autoimmune disease to a manifest one by altered TNF-α levels is the proposed pathomechanism.[7]

Various vaccines used in children and adults (aged 3 months to 90 years) have been reported to induce BP.[7] These include influenza, swine flu, tetanus toxoid, varicella zoster, pertussis, diphtheria, polio vaccines and in some cases a combination of multiple vaccine administration has been reported.[7] The pathomechanism of vaccine-induced BP is

Table 18.3: Possible mechanisms of drug-induced bullous pemphigoid[19]

Hypotheses	Mechanism
Two-step theory	Two drugs of the same class may induce bullous pemphigoid in a stepwise manner. In a susceptible person who is already sensitized to a drug, exposure to another drug of same group or with structural similarity may induce formation of anti-basement membrane antibody.
Immune dysregulation or reorganization	In some individuals, sudden immune dysregulation or reorganization leads to loss of control over a possible disease phenotype, which is normally suppressed. There may be an alteration in T-regulatory cell function causing suppression of "forbidden" B-cell clones. This may facilitate release of anti-BMZ antibody.
Molecular mimicry	Some drugs act by binding to RNA and various other transcriptional and translational regulators as is done by virus. Host immune system may recognize these drugs as microbial antigen; in susceptible individuals, this may lead to activation of $CD4^+$ T cells and an autoimmune mechanism starts.
Hapten	Some drugs may act as haptens that bind and modify basement membrane proteins. Thus, hidden antigenic sites are exposed and there are alteration in antigenic properties.
Direct injury	Thiol drugs may cause disruption of dermoepidermal junction (DEJ) directly by interacting with sulfhydryl groups in desmosomes.

poorly understood. It has been hypothesized that in predisposed individuals, inflammatory response due to vaccine administration may induce disruption of BMZ with production of specific antibodies.[7]

Various topical therapies [5-fluorouracil, PUVA, timolol eye solution, anthralin, coal tar, benzyl benzoate (30%), diclofenac gel, iodiphor adhesive band] have been reported to induce BP.[2,7] The exact mechanism of this phenomenon is not clearly understood. It has been postulated that there is exposure of BMZ antigens in case the epidermis is damaged. In genetically predisposed individuals, there is formation of anti-BMZ antibodies, followed by activation of inflammatory cascade to result in BP.

Clinical Features

The disease starts approximately by 3 months of initiation of the offending drug. Although clinical picture of drug-induced BP remains essentially similar to idiopathic disease, there may be subtle points of difference. Unlike in classical BP, younger patients are the usual sufferers.[2]

Face, lower legs (Figs. 18.4 A and B), and mucosa (oral and conjunctival) are commonly affected.[2] Evolution of bullae over erythematous or urticarial base is uncommon.[2,7] There may be target-like lesions on palms and soles.[2,7] Occasionally, Nikolsky's sign is positive.[2,7] Pruritus is usually intense.[2,7] The erosions heal without scarring.[7] Generalization of localized anogenital BP by TNF-α inhibitor etanercept has been reported.[21]

Despite considering all the above differentiating points, diagnosing drug-induced BP is difficult. There must be high level of suspicion, especially in elderly patients on multiple drugs. In such cases, history of a recently added new drug or change over to a new drug should be asked for.

Investigations

The histopathological features of drug-induced BP differ from the classical disease; subepidermal and intraepidermal splits and necrotic keratinocytes are present.[7] The blister cavity fluid is rich in eosinophils and a dense dermal infiltrate composed of eosinophils, neutrophils, lymphocytes, and histiocytes is present.[7] DIF positivity is seen in 90% cases and findings are similar to idiopathic BP i.e. linear deposition of IgG and C3 along the BMZ.[7] IIF is positive in 75% cases of drug-induced BP.[7]

There are few hematological and biochemical markers detectable in patients with drug-induced BP. These include the following[7]:

- Peripheral blood eosinophilia.
- Increased soluble IL-2 receptors.
- Increased eosinophilic cationic protein and neutrophilic myeloperoxidase in sera and blister fluid.

Mast cell degranulation toward the offending drug may be demonstrable.[7]

Management

Withdrawal of the offending drug is the first step in management. These cases respond well to topical and systemic corticosteroids. The dose of systemic corticosteroids required to control the disease is usually lower than that of idiopathic BP.[7] Addition of other immunosuppressive drugs is not required.[7]

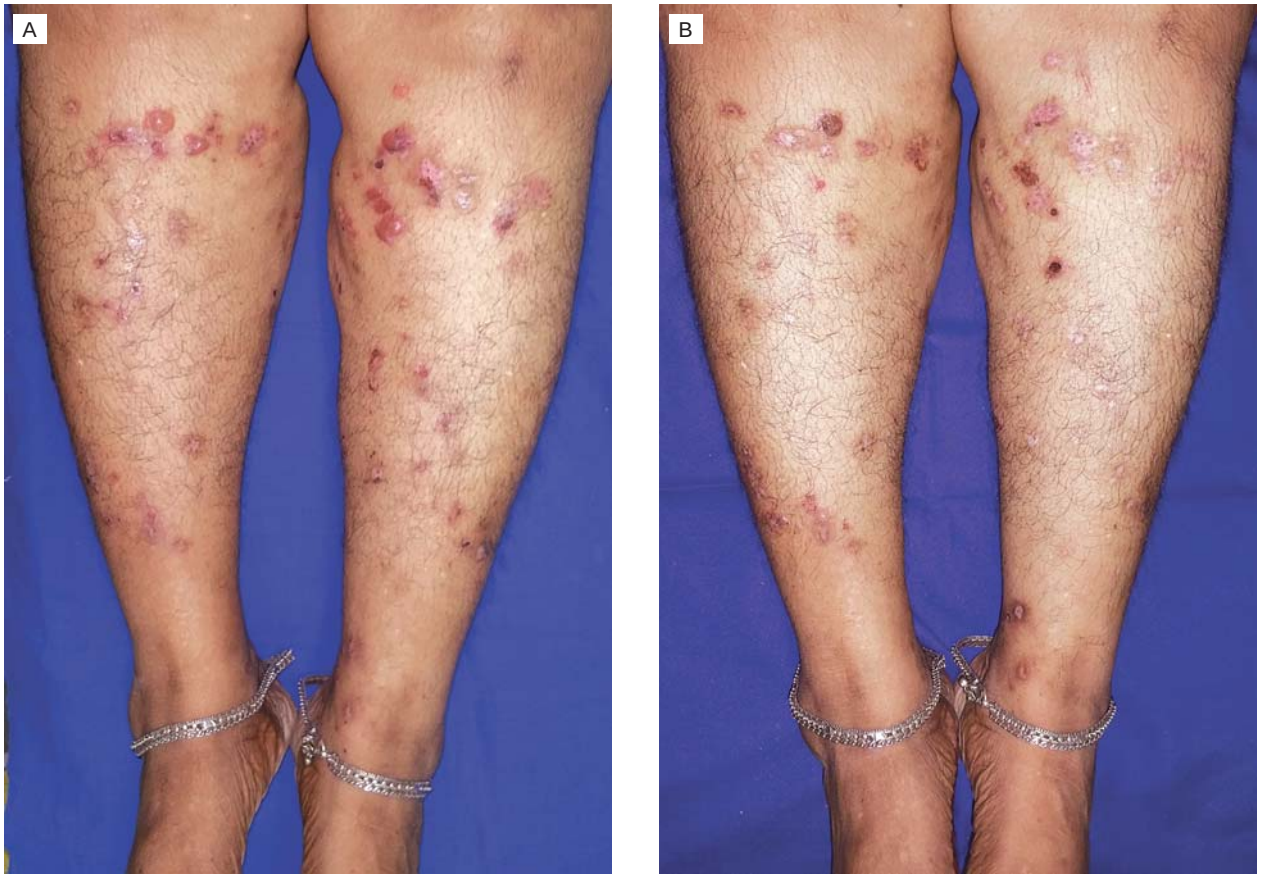

Fig. 18.4: (A) Bullous pemphigoid lesions in a patient on hydrochlorothiazide; (B) Resolution of lesions on discontinuation of hydrochlorothiazide.

Prognosis

Prognosis of drug-induced BP is good. There is complete resolution of the lesions on withdrawal of the drug and management. Recurrence is not seen.

DRUG-INDUCED LABD

Unlike drug-induced pemphigus and BP, this disorder is less defined and comparatively uncommon. The most common causative drugs are vancomycin, captopril, and co-trimoxazole in order of frequency.[2,22] The onset of skin lesions is by 2–4 weeks of the initiation of the drug. There are generalized polycyclic clusters of bullae, often arranged in typical "string of pearls" appearance as in the idiopathic disease. However, the skin lesions of drug-induced LABD are more severe and lack mucosal lesions which are often present in the idiopathic form.[22,23] Targetoid lesions may be present on palms and soles.[23] Nikolsky's sign is positive and large areas of erosion are present simulating Stevens–Johnson syndrome/ toxic epidermal necrolysis (SJS/TEN).[2,22]

Pathomechanism of drug-induced LABD is not clear. Similar to other drug-induced autoimmune bullous diseases, drug "acting as a hapten" theory and "exposure of hidden BMZ antigens by the drugs" have been suggested.[24]

Histopathological and DIF findings are comparable to the idiopathic disease.[22] However, focal necrotic keratinocytes may be more frequently seen in drug-induced cases.[22] When large area of denudation is present in a case of suspected SJS/TEN, it is preferable to undertake a DIF study to rule out drug-induced LABD where linear immune deposit (IgA) is observed at the DEJ.[2] IIF may be positive but evidence from reported cases suggests that frequency of IIF positivity is far lower in drug-induced LABD as compared to the idiopathic form. The lesions may resolve spontaneously by 5 weeks of drug withdrawal.[2] Dapsone and other sulfonamides have been used to treat some cases.[23] Recurrence is not seen.

DRUG-INDUCED PSEUDOPORPHYRIA

Pseudoporphyria is a condition where bullous lesions appear in photoexposed body parts simulating porphyria cutanea tarda (PCT), but there is no biochemical evidence of the disease.[25] This entity was initially described by Zelickson[10] in patients on therapy with nalidixic acid. As it was commonly seen in

patients with chronic kidney disease on hemodialysis, the term "bullous dermatosis of hemodialysis" was used.[25] Later it was found to be associated with intake of various photosensitizing drugs and clinical, histopathological, and immunological similarities with PCT were found. However, as these patients do not have biochemical evidence of abnormal porphyrin metabolism and it is absent in serum, urine or stool, the term "drug-induced pseudoporphyria" was coined.[25]

Pathomechanism

Pathomechanism of this condition is poorly understood. Phototoxic drug metabolites produced in genetically susceptible individuals may induce formation of bullae.[25] The solar light spectrum inducing pseudoporphyria is in the ultraviolet range and possibly visible light also.[25]

Drug-induced pseudoporphyria is common in patients with chronic kidney disease; more so in patients on hemodialysis rather than on peritoneal dialysis.[25] In these patients, role of reactive oxygen species has been suggested in the pathogenesis of pseudoporphyria.[25] Red blood cells in these patients are glutathione deficient, which make them prone to oxidative stress and increases the susceptibility to UV light.[25] The aluminum hydroxide content of dialysate fluid may impair clearance of plasma-bound porphyrin precursors which tend to get deposited in the skin.[25]

Clinical Features

This condition is common in middle-aged patients with mean age of 50 years at presentation.[26] Patients with chronic renal failure on hemodialysis or peritoneal dialysis are more prone to develop this disorder.[9] The skin lesions are in the form of tense bullae on photoexposed areas, most commonly on dorsa of hands and feet.[26] Forearms, face, and neck may also get involved. The lesions heal with scarring and milia formation.[26] Unlike in PCT, hyperpigmentation, hypertrichosis, and sclerodermoid plaque are not the usual findings.[25]

Investigations

In histopathology, drug-induced pseudoporphyria shows subepidermal cleft formation and festooning of dermal papillae. DIF study shows granular deposit of C3 along DEJ and around the dermal blood vessels. Periodic acid–Schiff (PAS) staining shows deposition of PAS-positive, diastase-negative, hyaline material along DEJ and in the walls of the dermal blood vessels. Plasma porphyrin levels are normal. Uroporphyrin and coproporphyrins are not demonstrable in urine and stool specimens. In all patients with drug-induced pseudoporphyria, true porphyria must be ruled out. In patients with chronic kidney disease, serum porphyrin level tends to be higher than that in normal individuals.[25]

Differential Diagnosis

Drug-induced pseudoporphyria has to be differentiated from sub-epidermal autoimmune bullous disorders such as BP and epidermolysis bullosa acquisita (EBA).[25] EBA is characterized by linear deposit of IgG and C3 at the DEJ.[25] IIF from patient's serum demonstrates circulating autoantibodies in case of BP and EBA.[25] Histopathological evidence of thickness of dermal blood vessel walls is a point to differentiate pseudoporphyria from PCT. This is a consistent finding in PCT, but rarely found in pseudoporphyria.[25] Porphyrin profile is normal or near normal in patients with pseudoporphyria but may be marginally raised if there is concomitant chronic kidney disease, especially if the patient is on hemodialysis.[25]

Treatment

Strict photoprotection is suggested in these patients and broad-spectrum sunscreen should be used. Oral chloroquine has been used as a systemic photoprotecting agent. Withdrawal of the causative drug results in gradual resolution of the lesions by an average duration of 8 weeks.[25] In dialysis-induced pseudoporphyria, use of glutathione precursor N-acetylcysteine (800–1200 mg/day, orally, for 8 weeks) has been used successfully with clinical resolution of skin lesions.[9,25]

LEARNING ESSENTIALS

- Drug-induced bullous disorders are rare.
- Clinical features and laboratory features may be identical to the idiopathic disease.
- Drug-induced LABD may simulate SJS/TEN clinically and DIF study should be undertaken for differentiation.
- Self-resolution is common after drug withdrawal, except in drug-triggered pemphigus which may persist or recur.
- Treatment of these disorders is easier than the idiopathic forms and adjuvant immunosuppressive therapy is not required.
- Drug-induced pseudoporphyria is common in patients with chronic kidney disease, more so among those on hemodialysis.

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Chapter

19

Symmetric Drug-Related Intertriginous and Flexural Erythema

Feroze Kaliyadan

SUMMARY

Symmetric drug-related intertriginous and flexural erythema (SDRIFE) is a drug reaction characterized by a benign, self-limited, symmetrical, erythematous, rash involving the gluteal region and other flexural areas. A number of drugs have been associated with SDRIFE. This chapter discusses nomenclature, clinical features, pathophysiology, and management of SDRIFE.

INTRODUCTION

Symmetric drug-related intertriginous and flexural erythema (SDRIFE) is a benign and self-limited drug-induced intertriginous eruption characterized by a symmetrical erythematous rash involving the gluteal region and other flexural areas, without any systemic involvement. SDRIFE is considered to be a subtype of the baboon syndrome (BS).[1] BS is considered to be a variant of systemic contact dermatitis characterized by well-defined erythematous rashes affecting the buttocks, upper inner thighs, and axillae. The term "baboon syndrome" (named after the red-bottomed baboon) was introduced in 1984 by Anderson et al. to describe a bright erythematous, intertriginous rash induced by mercury in patients with previous sensitization to mercury.[2]

BS caused by systemic medication, without previous sensitization, is now labelled as SDRIFE.[3]

CLASSIFICATION AND TERMINOLOGY

The term SDRIFE was first proposed by Häusermann et al. because they felt that the pathogenesis in this condition is different from systemic contact dermatitis. Besides, the term "baboon" itself was deemed to be possibly offensive.[3] Another less commonly used term for the same is drug-related baboon syndrome (DRBS). SDRIFE, by definition is not associated with a known history of cutaneous sensitization.[1] Ozkaya et al. proposed a general classification of BS into three broad groups:

BS-Type 1:	Contact allergen–induced BS (excluding drugs)
BS-Type 2:	Contact allergic drug–induced BS
BS-Type 3:	Non-contact allergenic drug–induced BS (which corresponds to SDRIFE)[4]

As of now, the most accepted terminology for drug-induced BS, without a previous history suggestive of sensitization is SDRIFE.

CLINICAL FEATURES

The temporal association with drug intake is typical of SDRIFE. The onset of rash is usually within 2 days of exposure to the drug.[1,3,4] There have been isolated reports of longer durations after the exposure (up to 4 days).[5] Bright erythema affecting the gluteal regions in a symmetrical manner is the classical clinical presentation (Fig. 19.1). Any of the other flexures can be affected-the inguinal area (Fig. 19.2), axillae, and the neck being the most commonly affected areas. The lesions may rarely show ulceration (Fig. 19.3). The primary morphological appearance is in the form of diffuse erythema, but there can be associated papules and rarely pustules and vesicles.[3] Rarely, there may be involvement of the mucosa, face, palms, and soles.[1] A review of literature reveals no specific predisposition for the development of SDRIFE based on age, sex or race. Also there is no association with other significant skin or systemic diseases.

Diagnostic Criteria

Five diagnostic criteria have been proposed by Häusermann et al.[3]

1. Exposure to systemic drug at first or repeated dose (contact allergens excluded)
2. Erythema of the gluteal/perianal area and/or V-shaped erythema of the inguinal/perianal area
3. Involvement of at least one other intertriginous/flexural localization
4. Symmetry of affected areas
5. Absence of systemic symptoms and signs

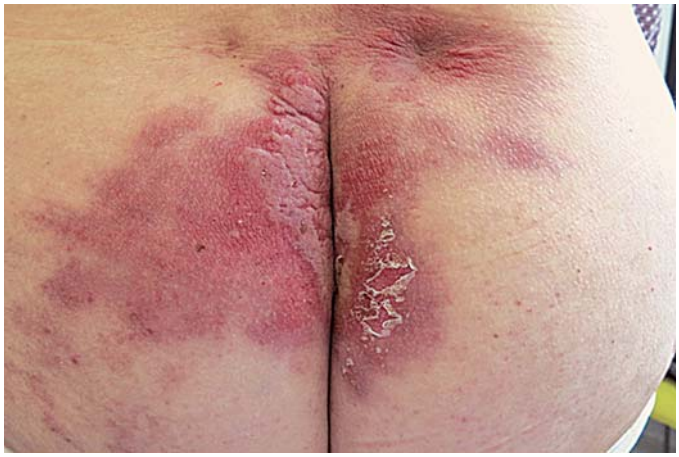

Fig. 19.1: SDRIFE lesion on buttocks due to paracetamol. (Courtesy of Professor Uwe Wollina, Dresden, Germany.)

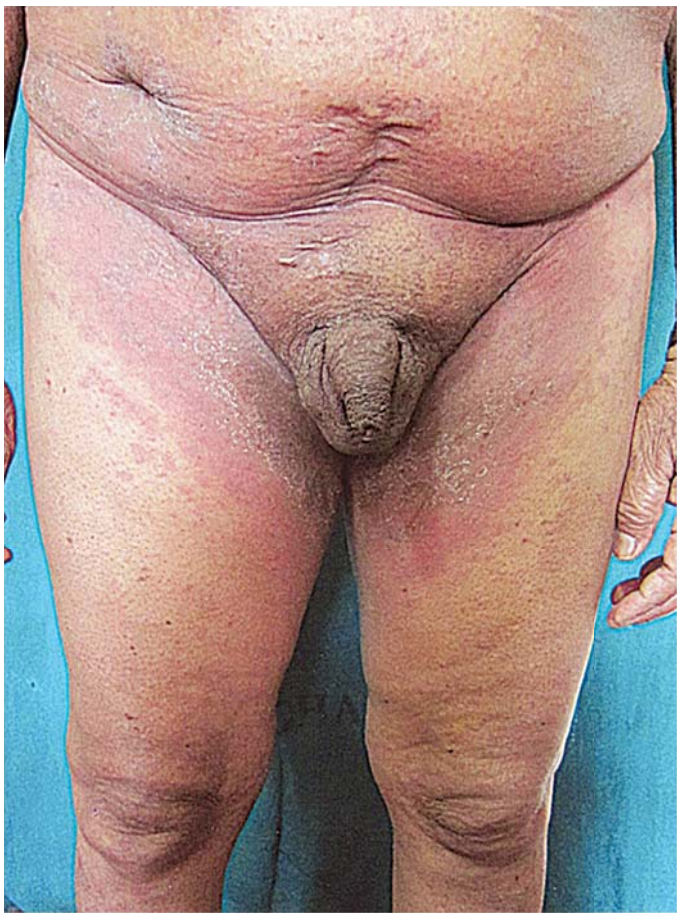

Fig. 19.2: SDRIFE lesions in groin due to allopurinol. (Courtesy of Dr. Bela Shah, Ahmedabad.)

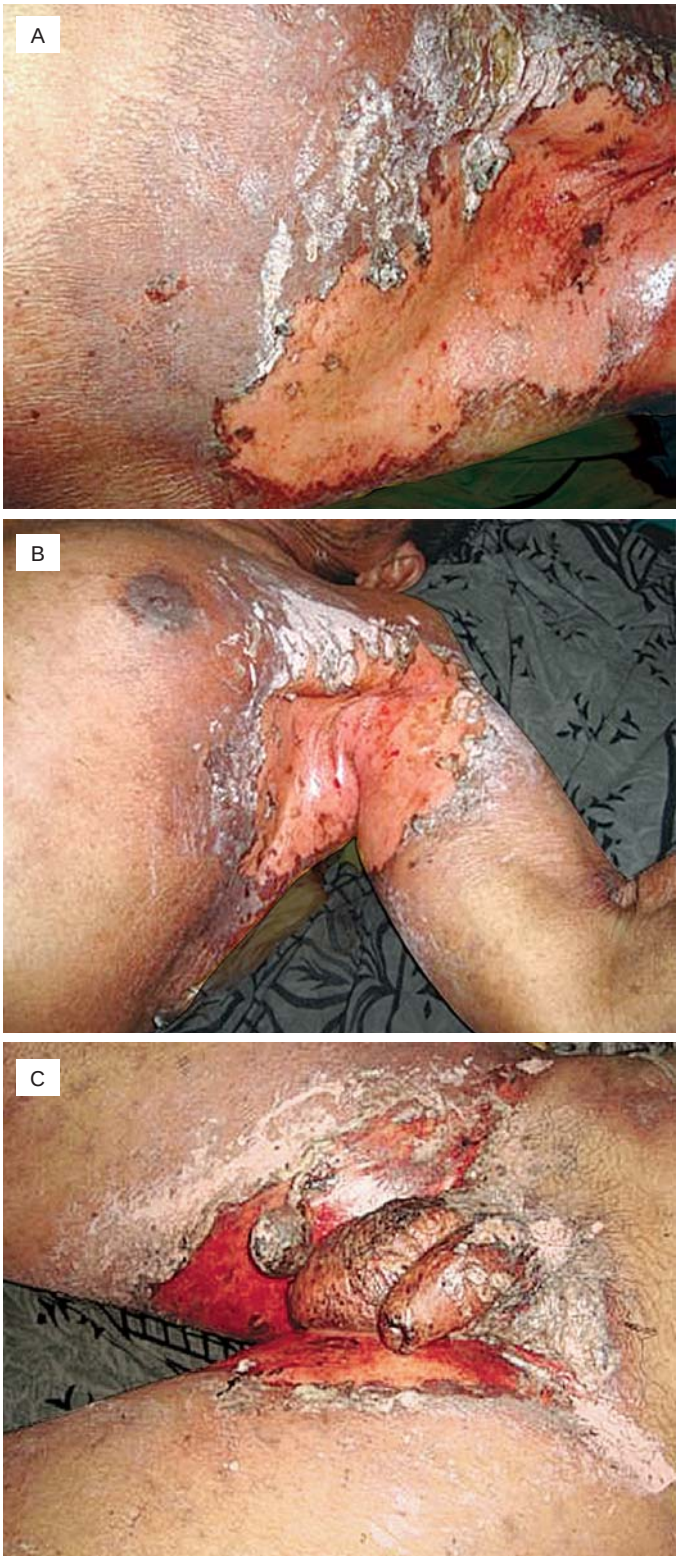

Fig. 19.3: (A–C) SDIFE, with unusually erosive lesions in axillae and groin in a patient taking diclofenac. (Courtesy of Dr. Anza Shan, Kozhikode.)

PATHOGENESIS

A T-cell mediated delayed hypersensitivity has been suggested to be the primary mechanism involved in the pathogenesis of both BS and SDRIFE. This is based on demonstration of $CD4^+$ T-cell infiltration in the dermis in skin biopsies of patients with BS and also based on positive patch tests and lymphocyte transformation tests (at least in some patients).[6–11] However, as of now there is no clear explanation for the peculiar distribution of the skin lesions in BS/SDRIFE. One hypothesis is that BS/SDRIFE might be a manifestation of a recall-like phenomenon in areas of previous intertriginous inflammation (such as diaper dermatitis in infancy). Another suggestion is that the relatively higher concentration of eccrine glands in the intertriginous areas may lead to a higher excretion of the drug in these areas. Mechanical occlusion might also have a possible role in determining this particular distribution.[6–8]

Drugs Associated With SDRIFE

A wide variety of drugs have been implicated in causing SDRIFE (Table 19.1). The most common group implicated is β-lactam antibiotics, of which amoxicillin is the most commonly reported agent.[6]

Differential Diagnosis

The typical pattern and a history of drug intake should make one strongly think of SDRIFE. However, all intertriginous eruptions must be considered in the differential diagnosis.[1,3,4,6]

- Systemic contact dermatitis (classical BS): Essentially being a systemic allergic contact dermatitis, there is a history suggestive of sensitization and patch testing is usually positive. Common causes are metals (especially nickel and mercury), plants and topical medicines.
- Acute generalized exanthematous pustulosis (AGEP): Rarely, SDRIFE may be associated with pustules and vesicles as in AGEP but lesions tend to be less confluent. Absence of systemic toxicity, and lesions restricted to flexures are features strongly suggestive of SDRIFE.
- Other conditions that can be considered in the differentials include intertrigo, tinea cruris and flexural psoriasis. The abrupt onset of lesions, short duration, history of drug exposure and the difference in the morphology of the skin lesions is usually sufficient to differentiate SDRIFE from these conditions. A rare condition that presents similar to SDRIFE is a chemotherapy induced intertriginous rash seen in the pediatric age group. The main difference from SDRIFE is that the lesions can appear after a longer duration as compared to the SDRIFE, which usually occurs within a couple of days of drug exposure. It is possible though that some of these cases were actually SDRIFE itself.[43]

Table 19.1: List of drugs associated with SDRIFE

Group	Drug
Antibiotics	Amoxicillin/clavulanate[4,12,13]
	Penicillin[14]
	Ampicillin[15]
	Ceftriaxone, cefuroxime, cephalexin[13]
	Penicillin V[16]
	Pivampicillin[17]
	Roxithromycin[18]
	Clindamycin[8,19]
	Metronidazole[20]
	Sulfamethoxazole/trimethoprim[21]
Others	Paracetamol[22]
	Allopurinol[23]
	Deflazacort[24]
	Hydroxyurea[25]
	Naproxen[13]
	Oxycodone[13]
	Loflazepate[26]
	Intravenous immunoglobulin (IVIg)[10]
	Mitomycin[27]
	Terbinafine[28]
	Cetuximab[29]
	Iodinated/barium-containing radiocontrast media[13,30]
	Hydroxyzine[31]
	Risperidone[32]
	Rivastigmine[33]
	Telmisartan-hydrochlorothiazide[5]
	Valacyclovir[34]
	5 Fluorouracil[35]
	Etonogestrel/ethinylestradiol (vaginal ring)[36]
	Infliximab[37]
	Zoledronic acid[38]
	Everolimus[39]
	Etoricoxib[40]
	Ranitidine[41]
	Diclofenac[42]

Note: Some of the case reports related to causative drugs were published before the nomenclature of SDRIFE was established, but on review the cases fit in with the criteria of SDRIFE.

Assessment and Investigations

The diagnosis of SDRIFE is largely based on its clinical presentation (Fig. 19.4). It is important to keep the possibility of SDRIFE in mind whenever faced with an intertriginous rash of abrupt onset. Although the condition is benign and self-limited, it is best to pinpoint the causative drug in each case. The assessment of temporal association usually helps in the identification of the causative drug. Problems can arise when the patient has taken multiple drugs.

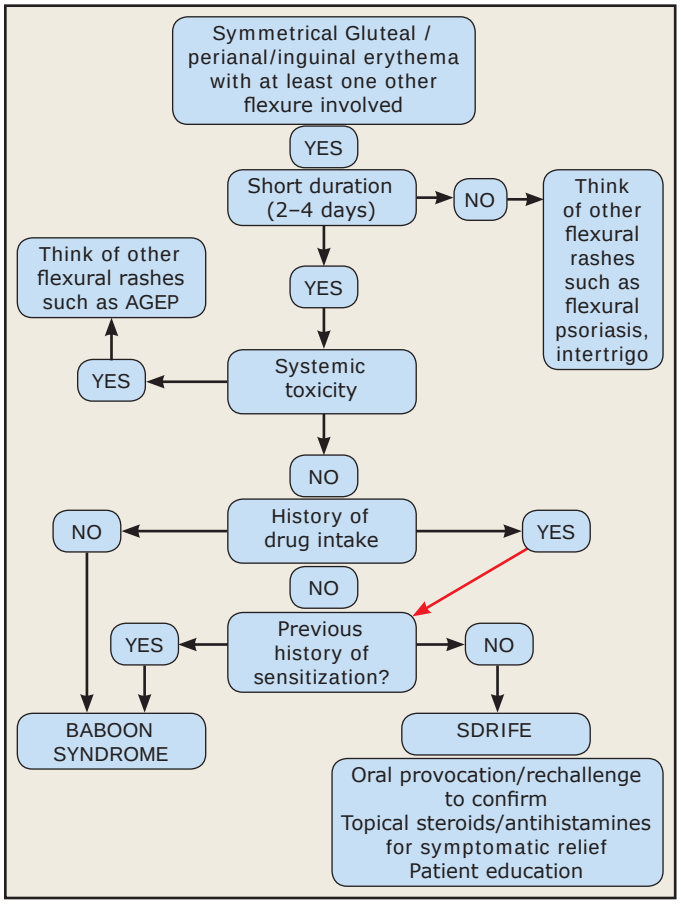

Fig. 19.4: Algorithm depicting clinical approach to SDRIFE.

A detailed history is essential. Important points not to be missed include:

- Any recent drug exposure
- History of contact sensitization
- History of positive patch test results
- In case of any plausible exposure to drugs, establish a clear time line for the events
- History suggestive of specific dermatological conditions such as intertrigo, psoriasis, and Hailey-Hailey disease that can affect the intertriginous areas

The dermatological examination focuses on the distribution and morphology of the lesions. All flexures are to be examined in detail.

Histopathology is not specific. Similar findings are seen in both BS and SDRIFE. Most common findings include a perivascular and sometimes periadnexal lymphohistiocytic infiltrate. The infiltrate sometimes might be mixed, involving neutrophils, eosinophils, and mast cells. Interface dermatitis with basal cell degeneration, subcorneal pustules, and spongiosis is also seen in some cases.[3,5,34,37,44]

Patch and prick testing in general are not always conclusive in the diagnosis of SDRIFE, although some of the cases do show a positive patch test reaction to the suspected drug.[40] Oral provocation tests/ rechallenge has been shown to elicit similar lesions in some cases and continue to be the gold standard for confirming the causative drug.[7,14,32,34] However, these should be attempted only in cases of essential drugs with no available alternatives.

Treatment

SDRIFE is self-limited. The most important step is to stop the offending drug. In case the drug is being substituted with an alternative, the possibility of cross-reactions must be kept in mind.[40] Symptomatic management with topical steroids and antihistamines can be given.[37] The patient must be educated regarding the possibility of recurrence with the same drug or other cross-reacting molecules. The lesions usually heal without leaving any significant post-inflammatory pigmentary changes although hyperpigmentation may persist for some time in a few cases.[4]

LEARNING ESSENTIALS

- SDRIFE is characterized by a drug-induced symmetrical erythematous rash involving the gluteal region and other flexural areas, without any systemic involvement. The dermatologist must keep the possibility of SDRIFE in mind in any case involving gluteal and flexural rash of sudden onset.
- The rash of SDRIFE and BS has the same morphological appearance. The distinction between SDRIFE and BS is mainly based on the concept that SDRIFE is not associated with previous sensitization.
- A detailed clinical history is essential to pinpoint the causative drug.
- Newer drugs continue to be reported as possible causes of SDRIFE. The dermatologist must be aware about SDRIFE and the medications causing it, to enable quicker diagnosis and optimal management.
- Patch testing is not conclusive; the investigation of choice is oral rechallenge /provocation test.
- SDRIFE is benign and self-limited. Topical corticosteroids and antihistamines can be used for symptomatic relief. Patient education is very important, especially in preventing recurrences.

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Chapter

20

Acneiform Drug Eruptions

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SUMMARY

Acneiform eruptions are acne-like, drug-induced eruptions, characterized by papules or pustules, with no comedones. Some drugs that cause acneiform eruptions include adrenocorticotropic hormone (ACTH), androgenic hormones, anticonvulsants, steroids, antitubercular therapy (ATT), and epidermal growth factor receptor (EGFR) inhibitors. Diagnosis is essentially clinical, suggested by the history of drug intake, presence of monomorphic papulopustular lesions, absence of comedones, unusual age of presentation, and lesions at unusual site. Treatment options include withdrawal of the causative drug, benzoyl peroxide, topical or oral antibiotics, isotretinoin, and chemical peels.

INTRODUCTION

Acneiform lesions are defined as inflammatory follicular reactions that resemble acne vulgaris and present clinically as papules or pustules. The condition presents as monomorphic lesions, seen primarily on the upper parts of the body (namely, face, chest, upper back and arms). Unlike acne vulgaris, comedones are not seen.[1]

The basic criteria that determine acneiform eruptions include the following:[1]

- Sudden onset
- Worsening of existing acne lesions
- Monomorphic lesions
- Affliction of unusual sites
- Age of onset
- History of exposure to a potentially responsible drug

PATHOGENESIS

The mechanism by which each drug causes acneiform eruptions is variable. Possible explanations have been hypothesized depending on the drug's mechanism of action or target of action and their effects on natural pathways involved in idiopathic acne vulgaris (Fig. 20.1).

CLINICAL FEATURES

Though there are no specific criteria established to diagnose drug-induced acne or acneiform eruptions, there are several pointers that can help to differentiate the two entities (Table 20.1).

It is usually a de novo onset of an eruption in the absence of a history of acne vulgaris and can present either as an unusually severe acne flare in a patient with a history of mild acne vulgaris or as an aggravation of preexisting acne. The monomorphic pattern with a profusion of inflammatory pustules and papules with either a lack of or late appearance of comedones and cysts is classical.

A temporal association is crucial. The onset of acne after drug administration, improvement after drug withdrawal, or recurrence after drug reintroduction can establish the causative drug, though a specific time period for this to occur has not been defined.

DRUGS IMPLICATED

A list of drugs implicated has been mentioned in Table 20.2 and the common and important ones are discussed in detail in the following sections.

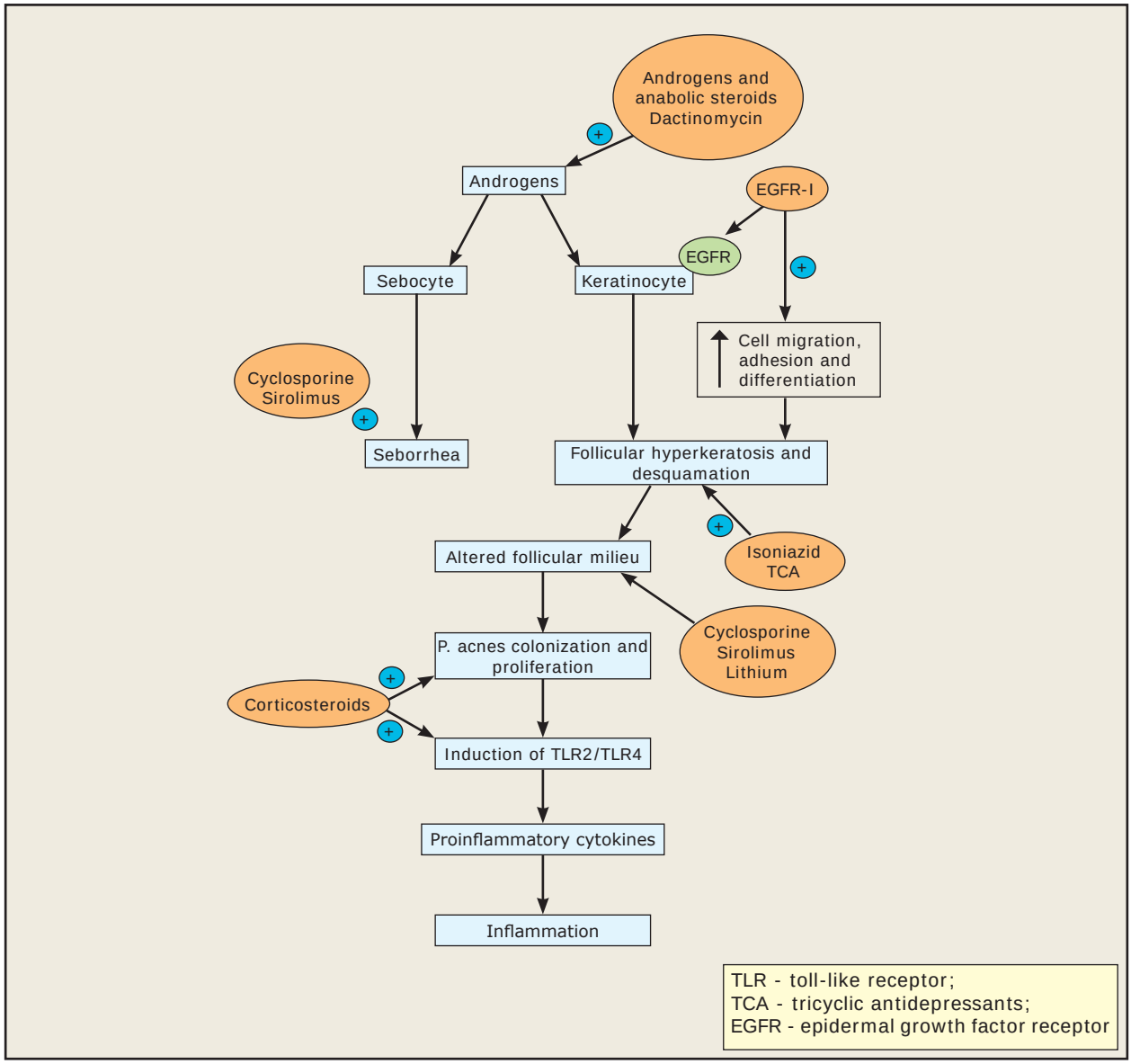

Fig. 20.1: Pathophysiology of acne and possible drug targets in causation of acneiform eruptions.

Table 20.1: Differentiating features between drug-induced acneiform eruption and idiopathic acne vulgaris

Drug-induced acneiform eruption	Idiopathic acne vulgaris
Monomorphic, inflammatory pattern of papules and pustules	Polymorphic pattern of comedones, pustules, cysts, and scarring
Lack of comedones and cysts or their late appearance	Comedones and cysts are characteristic skin lesions
Extend beyond seborrheic areas to include arms, trunk, lower back, and genitalia	Localized primarily on seborrheic areas such as the face and neck and, less commonly, on the upper back, chest, and arms
Can affect young children and adults >30 years of age	Commonly affects adolescents and young adults
Resistant to conventional acne therapy	Improves with conventional acne therapy
Onset after drug initiation, improvement after drug withdrawal, or recurrence after drug reintroduction	No causative relationship to drug therapy

HORMONES

Corticosteroids

Corticosteroids (Figs. 20.2, 20.3) can cause acneiform eruption and can be consequential to systemic (oral[2] or intravenous[3]), topical[4], and inhaled[5] corticosteroids.

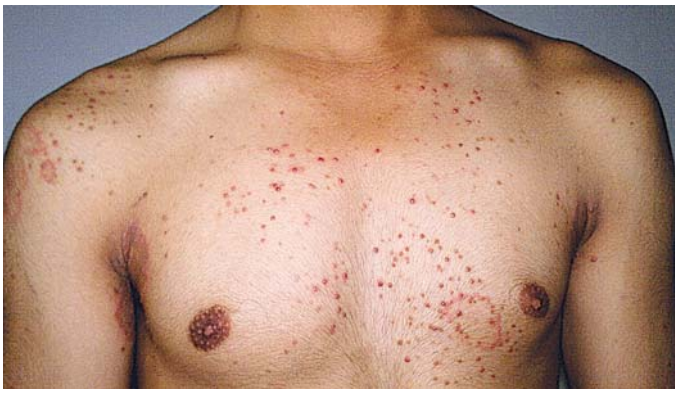

Fig. 20.2: Acneiform eruptions in a young boy due to oral corticosteroid abuse for tinea. Note the inflammatory monomorphic lesions on chest. Also seen are lesions of modified tinea on chest and in axillae.

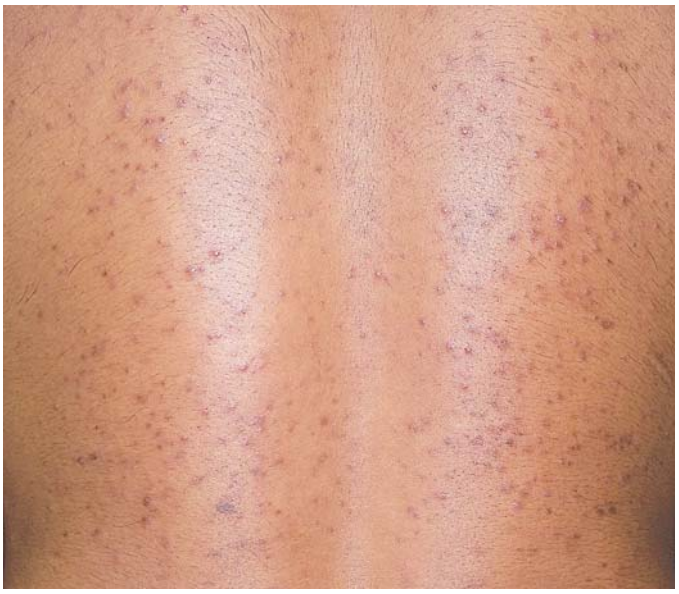

Fig. 20.3: Acneiform eruptions on back in a patient receiving triamcinolone injections for psoriasis.

Perioral (periorificial) dermatitis (Fig. 20.4) is an example of a corticosteroid-induced eruption seen around the mouth.[2] In India, probably the most common iatrogenic dermatological cause (in the authors' view) is the use of oral betamethasone pulse therapy and topical use of high-potency (class I and II) steroid creams.

These eruptions usually develop after a period of 2–4 weeks, but this may extend upto several months.[6] The lesions present as small, skin colored to pink and red dome-shaped inflamed papules and pustules, lacking comedones, distributed on seborrheic areas on face and trunk and with systemic use, involving the shoulders. The lesions typically present as papules rather than comedones; however, a histologic study confirmed that the incipient lesion is a microcomedone.

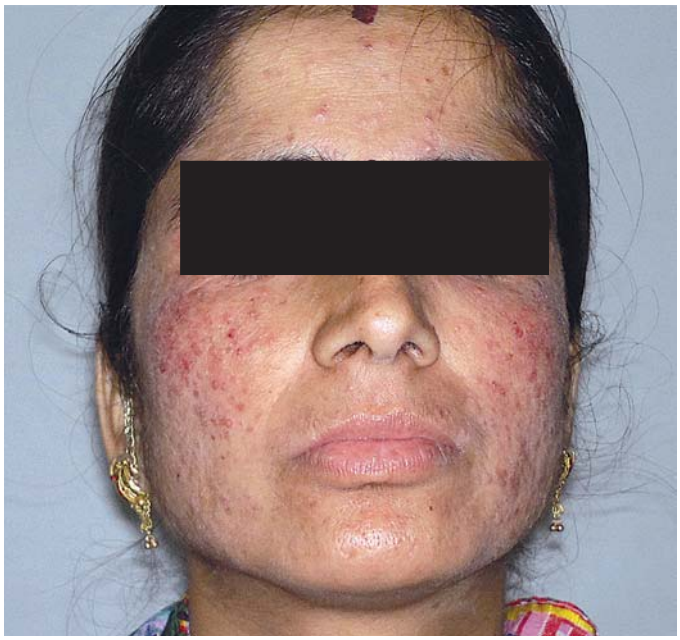

Fig. 20.4: Acneiform lesions on face due to topical steroid use as a fairness cream.

Pathogenesis

It is presumed to be due to alteration of free fatty acids in skin surface lipids with resultant increased numbers of bacteria within the pilosebaceous unit.[7] Another proposed mechanism is via an increase of toll-like receptor-2 (TLR-2) gene expression (in cultured human keratinocytes) which in turn is stimulated by Propionibacterium acnes, tumor necrosis factor-α (TNF-α), and interleukin 1α.[8]

Treatment

Topical retinoic acid 0.05% cream applied once or twice a day may clear the lesions within 1–3 months despite the continuation of high doses of corticosteroid. Oral antibiotics and other topical acne medications are also effective.

Androgens and Anabolic Steroids

Androgens (testosterone) and anabolic steroids affect sebaceous glands because of their structural similarity with endogenous androgens, which increase sebum production and lead to the development of idiopathic acne vulgaris.[9,10] This entity has been described

in young athletes who take anabolic–androgenic steroids to increase muscle mass ("body builder acne" or "doping acne").[11]

Hormonal Contraceptive

Hormonal contraceptives containing progestogens with androgenic activity or low-dose estrogens can cause or exacerbate acne. A large study in more than 2147 patients found that depot injections, subdermal implants, and hormonal intrauterine devices worsened acne, whereas combined oral contraceptives (COCs) improved acne.[12] Within COC categories, a hierarchy emerged based on the progestin component, where drospirenone was most helpful followed by norgestimate/desogestrel and levonorgestrel/norethindrone. Having said this, it must be noted that clinicians have been using desogestrel and levonorgestrel based OCP even for acne and they have a longer history of safe use than drospirenone. Another common cause (often missed by dermatologist on history) is acne after placement of levonorgestrel-releasing intrauterine device.[13] These patients develop inflammatory papules along the jaw 1–3 months after device insertion.

NEUROPSYCHOTROPIC AGENTS

Tricyclic Antidepressants

Among tricyclic antidepressants (TCA), amineptine is the prototype of acneiform eruption and it classically causes abrupt onset of monomorphic lesions composed of microcysts and macrocysts. The lesions occur many months or years after initiation of treatment and severity is related to dosage and duration of therapy. The drug might cause increased keratinization and lead to a morphology suggestive of neutrophilic eccrine hidradenitis with necrosis of eccrine glands.[14] Treatment includes suppression of dose or drug withdrawal, surgical removal of cysts, and administration of isotretinoin. Rare cases have also been reported with maprotiline and imipramine, though no case from India has been reported to date.[15]

Lithium

Lithium triggers neutrophilic cutaneous conditions such as neutrophilic folliculitis, and acneiform and psoriasiform eruptions.[1] Acneiform eruptions tend to occur within the first 6 months of therapy, and they are linked to lithium's tendency to increase circulating neutrophil chemotaxis, stimulate lysosomal enzyme release, and induce follicular hyperkeratosis.[16] A case has been reported from India where lithium caused hidradenitis suppurativa and acne conglobata during therapy, which subsequently decreased once lithium was stopped.[17]

Antipsychotic Agents

Aripiprazole is an atypical quinolinone antipsychotic agent with antidepressant properties. Acneiform eruptions have been reported to occur 10 days after initiating the medication and improve within 10 days after discontinuing it.[18]

Antiepileptics[19-24]

Phenytoin and phenobarbital are the two most common antiepileptics causing drug-induced acneiform eruption followed by lamotrigine and valproate.[19,20,21] Anti epileptic treatment has been reported to cause acne and enthesopathy.[19] Valproate can cause oligomenorrhoea and acneiform eruptions along with hyperandrogenism.[22] Phenytoin can cross the placental barrier and cause acneiform eruptions in the neonate.[23] Acneiform eruptions remit on withdrawal of the drug. Isotretinoin has been used to treat the acne and gum hypertrophy induced by phenytoin.[24]

VITAMINS

Vitamins B6 and B12

Megadoses of vitamins B6 and B12 (Fig. 20.5) have been reported to induce a facial acneiform eruption, which improves dramatically upon discontinuation.[25] The probable cause could be the iodine particles, which are used for vitamin B12 extraction, which induce hyperkeratinization. This could be another cause of bodybuilder's acne.[26]

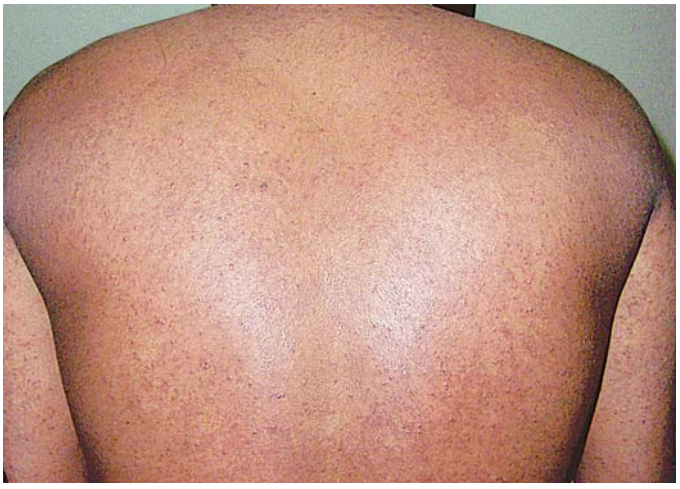

Fig. 20.5: Acneiform eruptions on trunk in a patient receiving Injection B6 and B12.

CYTOSTATIC AGENTS

Dactinomycin

Dactinomycin used mainly for testicular cancer, can occasionally cause acne. It is the androgenic properties

of dactinomycin which likely induces the acneiform eruptions, as serum levels of androstenedione, dehydroepiandrosterone and testosterone showed a rise and fall.[15] Lesions classically appear after the fifth day of treatment and are dose dependent. Lesions are usually severe.[27]

IMMUNOMODULATING DRUGS

Sirolimus

Sirolimus, an immunosuppressive drug often used after organ transplantation, has been associated with acneiform eruptions, involving mainly the seborrheic areas and occasionally the arms, forearms, neck and scalp.[28,29] The cause is the direct toxic effect of sirolimus on hair follicles, chemical modification of sebum and alteration of epidermal growth factor (EGF) and testosterone synthesis. It is postulated that sirolimus induces acneiform eruptions, predominantly in men, due to downregulation of epidermal growth factor receptors (EGFR) by testosterone suppression.[15,30]

Tacrolimus

A case of focal acne was reported during topical tacrolimus therapy for vitiligo.[31] Rosacea-like dermatitis has also been reported during treatment of facial inflammatory dermatosis with tacrolimus ointment.[32]

Cyclosporine

There have been reports of cyclosporine-associated acneiform eruptions that presents as severe nodulocystic acne and acne keloidalis nuchae.[15] The drug can modify the structure, function, and/or integrity of the pilosebaceous follicle, thereby inducing an acneiform eruption.[33] Ideally, the drug should be stopped; if not, isotretinoin can be used, along with careful monitoring of serum lipid levels.

Azathioprine

Occasional reports of acne because of azathioprine have been reported.[1] It has been reported in transplant patients[33] and when administered for multiple sclerosis.[34]

ANTITUBERCULAR DRUGS

Though it is commonly believed that antitubercular therapy (ATT) is one of the most common causes of acneiform eruption (Fig. 20.6), a study from India found that the overall incidence of acneiform eruptions in patients under ATT was only 1.42%.[35] The incidence of isoniazid, rifampicin, and ethambutol induced acneiform eruptions was 0.53%, 1.49%, and 0.63%, respectively. A possible explanation for the development of acne due to isoniazid is the competitive inhibition with its structural analogue niacin, which might predispose to follicular hyperkeratosis in some patients. Slow inactivators of isoniazid are thought to be more likely predisposed to these eruptions.[36] No possible explanation is available in cases of rifampicin and ethambutol-induced acneiform eruptions.[35]

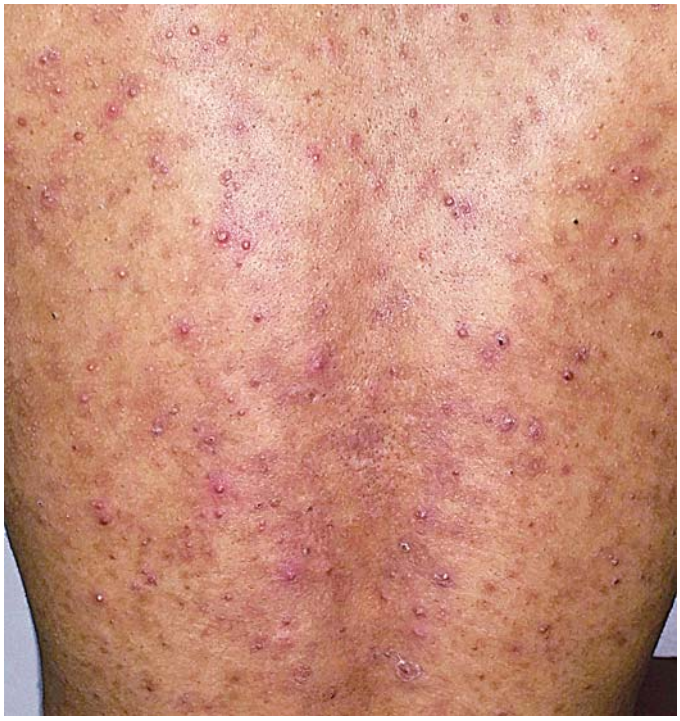

Fig. 20.6: Anti-tubercular treatment induced acneiform eruptions on back.

HALOGENATED HYDROCARBONS

Acneiform eruptions may originate from skin exposure to various industrial chemicals, such as fumes generated in the manufacture of chlorine and its by-products. These chlorinated hydrocarbons may cause chloracne, consisting of cysts, pustules, folliculitis, and comedones. The most potent acneiform-inducing agents include the polyhalogenated hydrocarbons, notably dioxin (2,3,7,8-tetrachlorodibenzodioxin).[37]

The most acne-prone locations to "chloracnegens" are the malar crescent (inferior and lateral to the eye) and the postauricular region.[38] The nose is characteristically spared by the eruption. In severe cases, lesions may involve the shoulders, chest, back, and eventually, the buttocks and abdomen. The genitalia can also be affected. Lesions can appear 2–3 months after first exposure and may last up to 15–30 years.

One of the most compelling illustrations of dioxin poisoning relates to the death of Ukrainian leader Viktor Yushchenko's who was poisoned by pure

dioxin. The compound was tasteless and he was allegedly poisoned by his own security chief ![39]

Cutting and lubricating oils, crude coal tar applied to the skin for medicinal purposes, heavy tar distillates, coal tar pitch, and asbestos are known to cause acneiform eruptions.[41] Acne venenata is another term applied to this process.

Inflammatory acneiform flares have been reported in association with ingestion of iodides and bromides.[42] The exposure occurs from thyroid medications, ingestion of cough expectorants, iodized salt, vitamin and mineral supplements and administration of radiocontrast dyes. The exact pathogenesis is not known. However, a follicular reaction due to neutrophil stimulation can explain the initial pustules (folliculitis- like reaction). Comedones occur subsequently, which are presumed to be due to hyperkeratotic reaction to chronic inflammation.[15] It is hypothesized that these compounds are eliminated by sebaceous glands leading to the eruptions.

TARGETED THERAPIES

Epidermal Growth Factor Receptor Inhibitors

Acneiform eruptions have been described in patients receiving targeted epidermal growth factor receptor (EGFR) inhibitor chemotherapy (Figs. 20.7 and 20.8A & B), affecting 66% of patients receiving gefitinib, 75% of patients receiving erlotinib, and 86% of patients receiving cetuximab during clinical trials.[43,44,45]

The pathogenesis of EGFR inhibitor induced acneiform eruptions is still not clear. Lichtenberger showed that EGFR is expressed in the basal layer of the epidermis.[45] When EGFR inhibitors are administered, it affects both EGFR expression in the tumor cells as well in the normal epidermal keratinocytes. This induces apoptosis, arrests cell growth, reduces cell migration, and increases cell adhesion and cell differentiation. All these processes induce keratinocytes to release inflammatory chemokines. These chemokines cause an inflammatory response with arrest of growth leading onto the skin manifestations like xerosis and maculopapular rash.[44] They are also known to unregulate the inhibitory effect of p 27 in the cell cycle and this allows hyperproliferation of stratum corneum in the follicular infundibulum, abnormal desquamation and follicular plugging.[45]

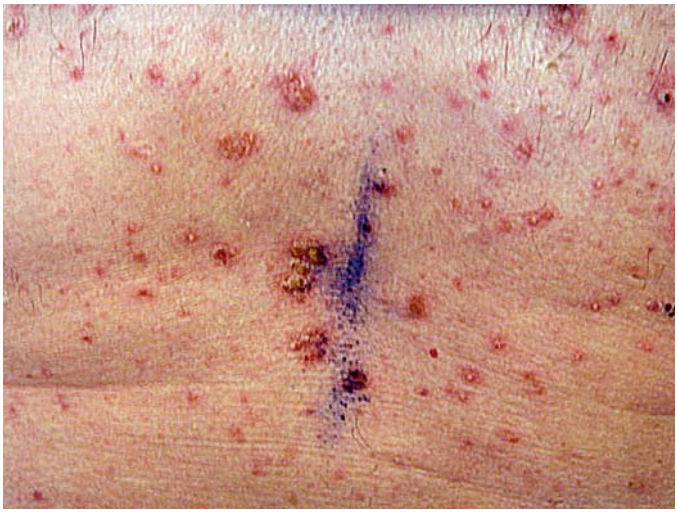

Fig. 20.7: Erlotinib induced acneiform eruptions on trunk. (Courtesy of Professor Uwe Wollina, Dresden, Germany.)

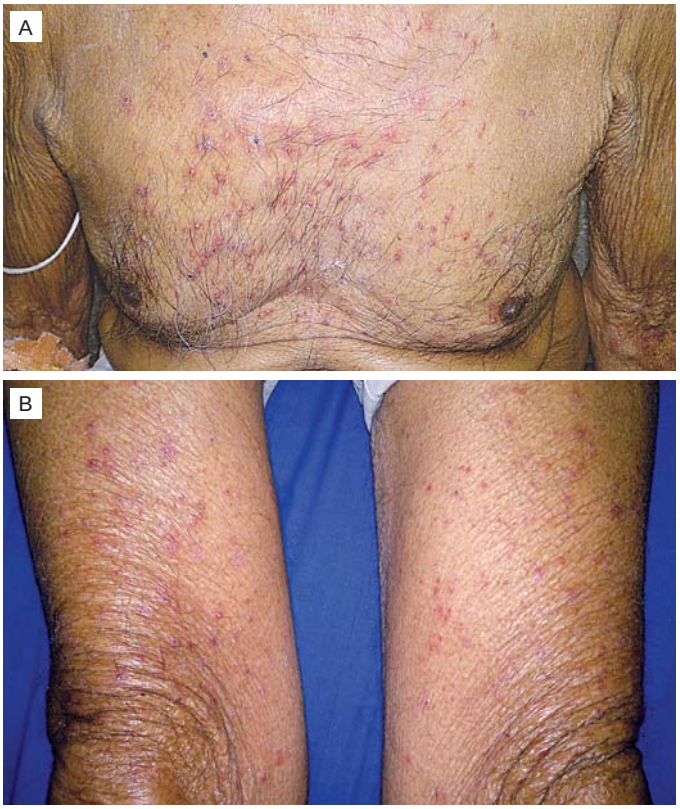

Fig. 20.8: Acneiform eruptions on chest (A) in an elderly on gefitinib for inoperable lung carcinoma; lesions on thighs; (B) in the same patient.

It is a dose-dependent drug reaction, which usually develops in the first 1–2 weeks, peaks at 3–4 weeks on therapy, and its intensity decreases after 2 weeks but can often persist over few months. Worsening of acneiform lesions can be observed immediately after each cycle of treatment.[1,15]

The constellation of symptoms has been labelled as the ***PRIDE complex*** *i.e.* "Papulopustules and/or paronychia, Regulatory abnormalities of hair growth, Itching and Dryness due to EGFR inhibitors".[46] Histologically, EGFR inhibitor–induced acneiform lesions display neutrophilic folliculitis and perifolliculitis. *P. acnes* has not been found in the affected hair follicles.[47] A few studies have reported that acneiform

lesion development is a prognostic factor for a good response to the treatment, with longer survival time, compared to those without cutaneous eruptions.[48] Tetracyclines (doxycycline and minocycline) are often tried to control severe eruptions. Figure 20.9 shows the three-step guideline for management of targeted therapy.

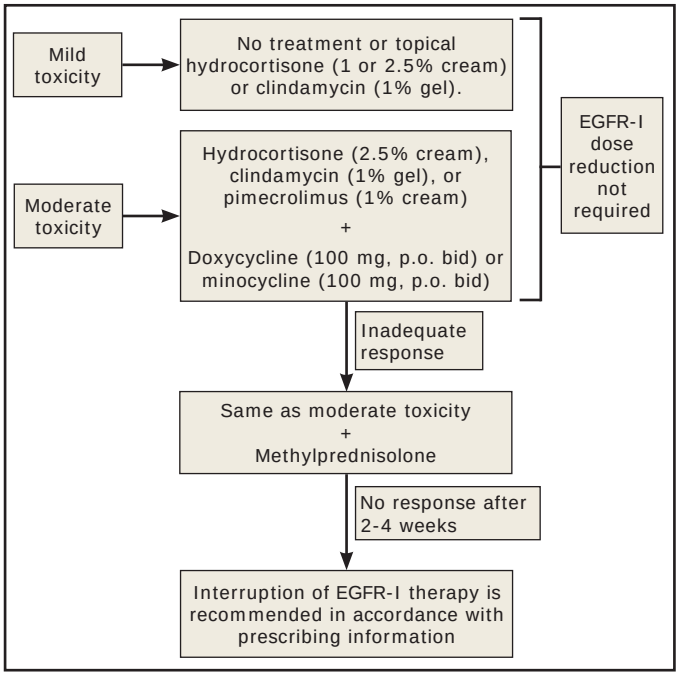

Fig. 20.9: Shows the three-step guideline for management of targeted therapy induced acneiform rash.

TNF-α Inhibitors

Of the TNF-α inhibitors, infliximab is the most commonly reported agent associated with an acneiform eruption.[49,50] Lenalidomide, a second generation of thalidomide, has major TNF inhibitory activity and has been reported to cause acute acneiform eruption in a multiple myeloma patient.[51]

MISCELLANEOUS DRUGS

Psoralen Plus Ultraviolet-A

Several cases of acne believed to be induced by psoralen plus ultraviolet-A (PUVA) treatment have been reported.[52] The common sites affected are the chest and back, perioral and the forehead. Acne-like eruptions on the face, induced by light, were first described using the term "light-sensitive seborrheic,"[53] whereas the term acne aestivalis (Mallorca acne) was used for papular eruption occurring after intense sun exposure in an anatomic distribution characteristic of acne vulgaris.[54]

Though western literature persists with the view that acne vulgaris usually improves during the summer months with exposure to sunshine, a study from India has confirmed that the converse is true and acne was seen to worsen in summers because of sweating, increased humidity, and rising temperature.[55]

Dapsone

Dapsone which acts via dihydrofolic acid inhibition can rarely cause acneiform eruptions. Paradoxically, topical dapsone has been tried as treatment of acne. A young female with preexisting mild facial acne vulgaris was treated with oral dapsone following poor response to oral tetracyclines. She soon developed acne fulminans and hemolysis, which resolved with prompt administration of high doses of vitamin C, oral prednisone, and intravenous methylene blue.[56]

Tetraethyl Disulfide (Disulfiram)

It is commonly used to treat chronic alcoholism. A repeated nodulocystic acneiform eruption involving the face, anterior chest and back has been reported, which resolves with withdrawal of the drug.[57]

Cardiac Medications

Some beta blockers like propranolol and nadolol[58] and quinidine[59] have been reported to cause acneiform eruptions that responded to topical erythromycin and topical benzoyl peroxide.

White Petrolatum

White petrolatum is used for its lubricating and moisturizing properties. However this can cause acne exacerbation or pustular reaction in predisposed individuals.[60]

MANAGEMENT

When a drug-induced acneiform eruption is suspected, it is important to take a thorough history, as new drugs or nonprescription drugs can cause acneiform eruptions.

A trial of drug termination should be tried in drug-induced acneiform eruption that persists or is severe. It is recommended to start termination of drugs that have been reported to cause the reaction or any drugs that were started in the 1–2 weeks previous to the initial eruption.

If drug termination is not feasible due to necessity of the drug, treatment of the drug-induced acneiform eruption can be considered with benzoyl peroxide, topical or oral antibiotics, or isotretinoin in certain cases. Non-ablative fractional laser has been shown to be effective in treating recalcitrant drug-induced acneiform eruptions.[37]

LEARNING ESSENTIALS

- Acneiform eruptions are the drug-induced eruptions resembling acne vulgaris.
- Most common cause of acneiform eruptions in India is corticosteroids.
- Drug induced acne is differentiated from acne vulgaris by history of prior drug intake, sudden appearance of lesions at an unusual age and sites, the presence of monomorphic papules or pustules and absence of comedones.
- Treatment involves stoppage of the inciting agent (drug), use of topical or oral antibiotics, retinoids and chemical peels.

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Chapter

21

Drug Induced Urticaria, Angioedema and Pruritus

Bela Shah • Abhay Mani Martin • Veenu Jindal

SUMMARY

Urticaria, also called hives, has a multifactorial etiology, of which drugs are an important subset. Urticaria is the second most common type of cutaneous adverse drug reaction after an exanthematous eruption. Urticaria, angioedema and anaphylaxis represent a spectrum of allergic disorders ranging from transient evanescent wheals to marked edema of subcutaneous tissue which sometimes progresses to life threatening anaphylaxis, if untreated. Patients presenting with anaphylaxis require urgent medical attention as this is a life threatening dermatologic emergency. The mechanisms of drug induced urticaria could be immunological (IgE or circulating immune complexes mediated) or non-immunological (complement activation, release of cutaneous mast cell mediators, or altered chemical pathways such as arachidonic acid metabolism). Drug induced pruritus is a lesser explored clinical presentation which is often poorly recognized due to lack of awareness.

A drug list is an absolute necessity in the evaluation of suspected drug induced pruritus or urticaria. Diagnosis is ideally done by rechallenge or *in vitro* testing but may be impractical in the clinical setting. Treatment of drug induced pruritus and urticaria include antihistamines and withdrawal of the drug, whereas angioedema and anaphylaxis are life threatening and hence may need adrenaline and/or corticosteroid administration. Future administration of the drug needs to be avoided by patient.

INTRODUCTION

Urticaria is a cutaneous reaction characterized by transient, pruritic, erythematous wheals of varying sizes caused due to superficial dermal edema. The individual lesions resolve rapidly usually within 24 hours.[1] Angioedema refers to deep dermal or subcutaneous swellings which are painful rather than being itchy. It may be potentially life-threatening when the pharynx or larynx is involved. It usually lasts for 1-2 hours, although it may persist for 2-5 days. Rarely, it can precede the development of an anaphylactic reaction.[1] Anaphylaxis is an acute, potentially life-threatening, multisystem reaction affecting the cutaneous, respiratory, gastrointestinal and cardiovascular systems.[1]

Drug Induced urticaria (DIU) is often an important subset of etiologic factors in urticarial eruptions. They should be suspected when there is a sudden onset of transient wheals with or without pruritus following the intake or parenteral administration of drugs. A working knowledge of drugs causing urticarial eruptions is necessary to suspect a particular drug/drugs as an etiologic factor. As the clinical presentation is very similar to other urticarias, a detailed history and temporal correlation is essential to diagnose a drug induced eruption.

Generalized/localized pruritus can sometimes be a presentation of a drug reaction too and should be borne in mind as a differential diagnosis of pruritus. Oral rechallenge is possible in such cases but most patients and treating doctors are reluctant to do this, due to the risks involved in the procedure. Skin testing and in vitro testing can be done but has its limitations to their interpretation.

EPIDEMIOLOGY

Urticaria is the second most common drug rash after morbilliform rashes.[2] Drug induced urticaria (DIU) was seen in 0.16% of consecutive monitored hospital inpatients and accounted for 5.9% of all drug rashes

according to a study done in Berne, Switzerland. Penicillin followed by NSAIDs and trimethoprim-sulfamethoxazole were the commonly incriminated drugs in their order of prevalence.[3] In a study done at Boston, 5% of 15438 hospital inpatients were affected with urticarial eruptions and 1.5% had generalized pruritus as a presentation with amoxicillin being the most incriminated drug.[4] In a Finnish study, the rate was 18% and aspirin was the drug implicated the most.[5] Zuberbier et al., in a series of 109 patients, identified that 9.2 % of adult patients, who attended the emergency clinic had drug induced etiologic factor as the cause of urticaria.[6] Morturieux et al. identified preexisting infection in 80% of children with acute urticaria and hence noted that it is difficult to dissociate an infection induced urticarial eruption from drug induced etiology.[7]

In India, patients with adverse drug reactions have been studied in tertiary care settings. Pudukadan et al. reported the incidence of drug induced urticarial eruptions to be 9.8%.[8] in Puducherry, and Sharma et al. reported 17.3% in a study at Jammu.[9]

DIU is more likely to present as acute urticaria than as chronic recurrent urticaria.

A study concluded that 9% of 220 patients had chronic urticaria or angioedema caused by an adverse drug reaction.[10] Chronic urticaria, precipitated by drugs has been noted with drugs like NSAIDs and aspirin in 10-35% patients.[11-15] The evidence for aggravation of physical urticaria is however lacking. While an earlier report showed that aspirin did not precipitate physical urticaria,[11] a larger prospective study showed that aspirin can aggravate cholinergic and pressure urticaria in some patients.[15] Drug induced urticaria is also known to trigger a chronic cold contact urticaria.[2]

Several risk factors have been implicated in the predisposition to DIU and include atopy, female gender, third decade of life[13] and familial predisposition to aspirin intolerance.[14]

CLINICAL PRESENTATION

Drug induced urticaria is indistinguishable from other forms of urticaria. DIU may present clinically as acute urticaria, chronic urticaria, serum sickness like reaction, angioedema or anaphylaxis (Box 21.1). A specific history of drug intake prior to the eruption with urticarial wheals is a classical presentation. Dermal or subcutaneous swellings distributed focally or in a generalized fashion, which are more painful, suggest angioedema. Systemic symptoms like fever and arthralgia occur in serum sickness like reaction. Urticaria or angioedema may self-limit or progress to severe presentations like breathlessness, edema, hypotension, shock and sometimes even death and is called anaphylaxis.

Box 21.1: Clinical presentations of drug induced urticaria (DIU) and angioedema

Acute urticaria
Exacerbation of chronic urticaria
Exacerbation of physical urticarias
Serum sickness like reaction
Urticarial vasculitis
Contact urticaria
Angioedema
Anaphylaxis

Drug induced urticarial reactions may have acute or delayed presentations. The onset may range from a few minutes post drug intake to 36 hours, as occurs with a serum sickness like reaction. The remission after stoppage of the drug is also variable and may take several days.

Acute presentations are characterized by generalized, transient, itchy wheals (Fig. 21.1) that usually last less than 24 hours. The eruptions may start after a single exposure to the drug, after multiple exposures to the drug as well as after multiple uneventful, well tolerated exposures in the past. The rash occurs as new onset urticaria or exacerbation of a chronic or physical urticaria. The onset of lesions is more rapid than other drug eruptions and hence immediate medical attention is necessary in such cases.

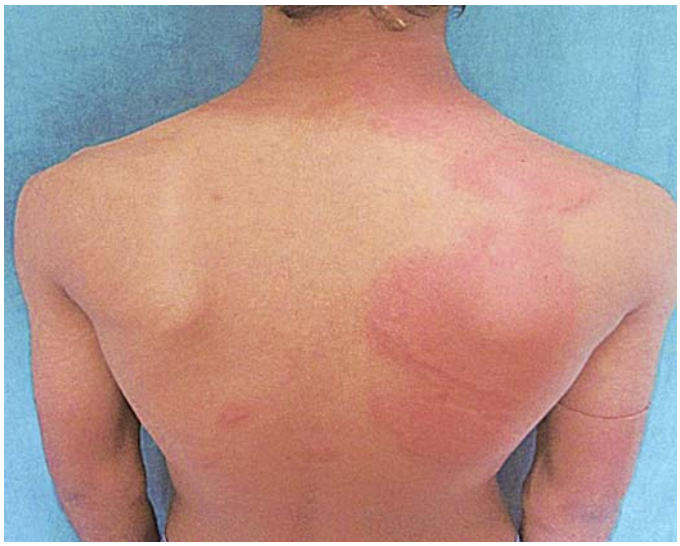

Fig. 21.1: Drug induced urticaria, induced by ciprofloxacin.

Delayed onset reactions occur with immune complex mediated, serum sickness like reactions. This can occur with drugs like penicillins, cefaclor, streptokinase and propranolol. It occurs 6-14 days after exposure

to the antigen (a drug). It presents with erythema of the sides of fingers, toes and hands. This is followed later by a distinctive morbilliform rash in two third of cases. Systemic symptoms like fever, constitutional symptoms, arthralgia and arthritis accompany the rash in nearly 50 % of cases.

Angioedema and anaphylaxis, though life threatening are relatively less common. Angioedema presents as raised tender dermal or subcutaneous swellings. They may be focal in distribution like the face, lips, forehead and extremities or generalized. Angioedema is most often noted with ACE inhibitors (Fig. 21.2 A) and non-steroidal anti-inflammatory drugs (NSAIDs) (Fig. 21.2 B). Anaphylaxis is dealt in detail in chapter 29.

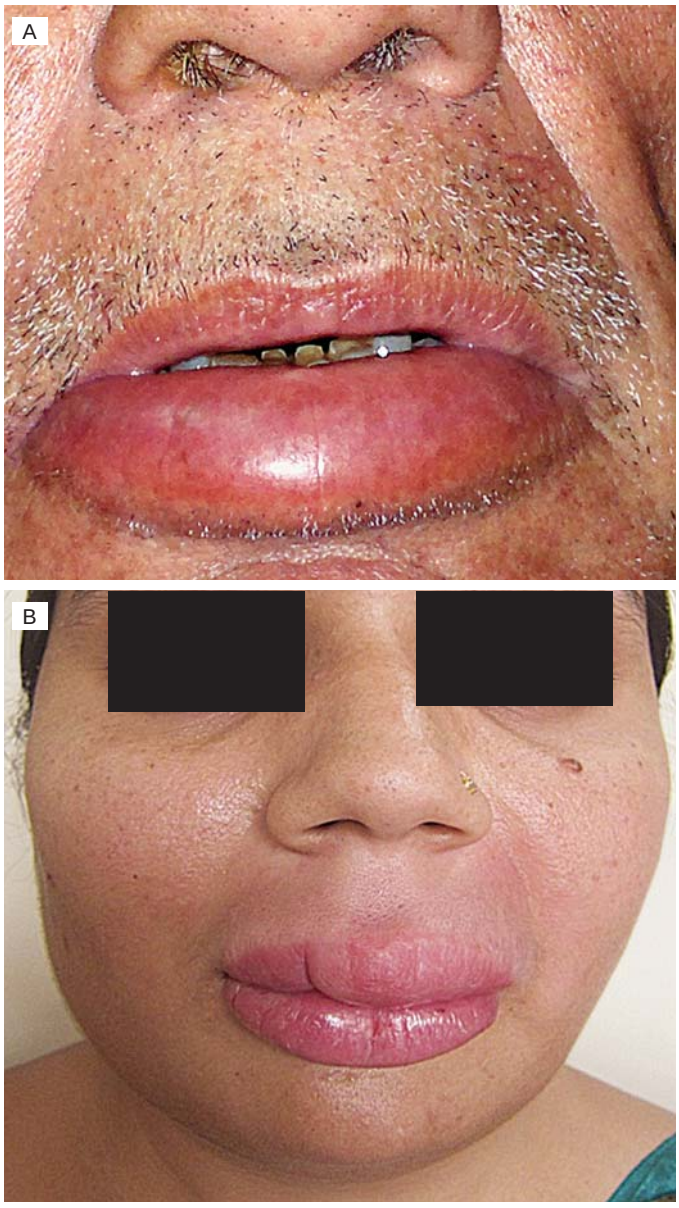

Fig. 21.2: Drug induced angioedema on lips in an elderly man (A) due to ramipril and in a lady (B) taking ibuprofen intermittently for her joint pains.

PATHOGENESIS

Drug induced urticarial eruptions can be due to immunologic or non-immunologic mechanisms.

The mechanisms are summarized in Table 21.1.

Immunologic Reactions

IgE Mediated Urticarial Reactions

IgE dependent reactions occur within minutes after drug exposure (immediate reactions) or within days of exposure (accelerated reactions). Penicillins are the commonest cause of IgE mediated reactions.[2] They are thought to result from release of chemical mediators from sensitized tissue mast cells or circulating basophils. Such mediators may include histamine, peptides such as eosinophil chemotactic factor of anaphylaxis (ECF-A) or lipids such as leukotrienes or prostaglandins. It is postulated that polyvalent drug protein conjugates, formed in vivo, cross link IgE molecules fixed to sensitized cells.[19]

Circulating Immune Complex Mediated (Serum Sickness-like Reaction) Urticaria

This was earlier called serum sickness as it developed following injection of foreign sera (e.g. horse antisera in diphtheria). However drugs are now currently the most common cause of serum sickness like reactions. This presents as fever, urticarial or papular rash, nephritis, arthritis, neuritis and edema.

In this reaction IgG- drug complexes deposited on vascular endothelium activate complement cascade resulting in formation of C3a and C5a anaphylatoxins that degranulate mast cells and basophils. Vasoactive amines and pro-inflammatory cytokines are released from basophils and mast cells, with resultant increased vascular permeability and attraction of neutrophil polymorphonuclear cells.[19] Antigen – antibody immune complexes cause the symptoms of the disease based on its target organ. Symptoms of this reaction take 6 days or more after exposure to the drug as this represents the latent period required to synthesize the antibody.[19-21]

This drug reaction presents as either as classical urticaria or urticarial vasculitis where lesions are painful and persist for more than 24 hours. Autoimmune diseases, infections, malignancy and complement and immunoglobulin abnormalities can have similar presentations.

Non Immunologic Reactions

Non immunologic reactions are non-immune mediated and do not fit into the classical Coombs and

Table 21.1: Mechanisms and clinical presentations of drug induced urticaria and angioedema

Immunologically mediated reactions			
Coombs and Gell hypersensitivity type	**Mechanism**	**Clinical presentation**	**Commonly implicated drugs**
Type 1 Hypersensitivity/ immediate reactions	Mediated by drug specific IgE on mast cells and basophils	Anaphylaxis and urticaria	Antibiotics (penicillins), anticonvulsants, cardiovascular drugs
Type 2 Cytotoxic reactions	Mediated by cell bound drug specific IgG, IgM and complement	Thrombocytopenic purpura	
Type 3 Immune complex reactions	Mediated by soluble drug specific IgG, IgA, IgM and complement	Serum sickness Urticarial vasculitis	Penicillins, antisera sulfonamides, thiouracils, cholecystographic dyes, diphenylhydantoin, aminosalicylic acid, and streptomycin
Type 4 Delayed type Hypersensitivity	Mediated by drug sensitized lymphocytes	Allergic contact dermatitis	Relevant for topically applied medicaments
Non immunologic reactions			
Kinin mediated reactions	Drug inhibits kinin degradation	Urticaria and angioedema	ACE inhibitors
Eicosanoid mediated reactions	Drug interferes with arachidonic acid metabolism	Urticaria and Angioedema	Aspirin, NSAIDs
Degranulation	Drug induces direct mast cell degranulation	Urticaria angioedema, anaphylaxis	Opioids, codeine, atropine, atracurium, rifampicin, polymyxin hydralazine, quinine, radiocontrast media, vancomycin, dextran
Combined immunologic (allergic) and non immunologic mechanisms (pseudoallergic)			
Contact urticarial reactions	Drug contact induces a. IgE mediated type I hypersensitivity reaction (IgE mediated histamine release) or b. Pseudoallergic reaction (Dermal mast cells are degranulated by direct action of the absorbed drug)	Urticaria and angioedema; rarely anaphylaxis	Oestrogen, progesterone, penicillin, gentamicin, neomycin, bacitracin, promethazine, benzophenone, latex, menthol, polyethylene glycol, cetyl stearyl alcohol
Allergies to excipients	They may be allergic or pseudoallergic	Urticaria and angioedema	Benzoic acid, butylated hydroxytoluene, sulfites, aspartame, coloring, tartrazine, and preservative

Gell classification of hypersensitivity disorders. Drug reactions that occur in relation to derangements in the kinin cascade, eicosanoid pathway and direct mast cell degranulation are included in this category.

The term *"pseudoallergy"* is sometimes used to address a clinical reaction resembling immediate hypersensitivity without involvement of the immune system. This overrides other terms like drug hypersensitivity, intolerance and idiosyncratic reaction and is the preferred term for several experts in Europe and the UK but is not favored by the American Association of Asthma and Clinical Immunology. There is no sensitization phase and therefore may occur with chemically and structurally unrelated compounds. They appear to be dose dependent and are characterized by slow onset of symptoms (within 24 hours with 50% of reactions occurring in the first 6 hours.) in contrast to IgE mediated reactions that occur within minutes of exposure.[22]

Eicosanoid Pathway Mediated Reactions

Drugs such as NSAIDS interfere with arachidonic acid metabolism. They cause activation of the lipoxygenase pathway (LOX) by inhibiting the cyclooxygenase (constitutive-COX-1 and inducible –COX-2) pathway resulting in overproduction of leukotrienes like LTC_4, D_4 and E_4 and reduction of PGE2 (that inhibits mast cell degranulation).[22,23]

Direct Mast Cell Degranulation

Binding of the drugs like codeine (prototype example) to mast cells cause direct degranulation to release mediators like histamine, proteases (tryptase, chymase), heparin, cytokines (IL-4, 5, 6, 13, GM-CSF, TNF-α, platelet activating factor, PGD_2, LTC_4).[22] This occurs with drugs like antibiotics (polymyxin B, vancomycin, ciprofloxacin, rifampicin), muscle relaxants (atracurium), atropine and radiocontrast media.[22] There is massive release of these mediators which may have fatal consequences.

Kinin Mediated Angioedema

Angioedema has been reported in 0.1-2% patients taking ACE inhibitors (ACEI).[24] Angiotensin Converting Enzyme Inhibitors (ACEI) convert angiotensin I to angiotensin II in the renin angiotensin aldosterone system and is also a kininase. Inhibition of ACE results in build up of bradykinin (due to reduced inactivation) which in turn increases vascular permeability and causes vasodilatation.[25,26]

Some common drugs implicated in urticaria are listed in the table (Table 21.2). The list is not exhaustive but only representative.

Table 21.2: Common drugs implicated to cause urticaria

Drug group	Common drugs
Antibacterials	Rifampicin
Antifungals	Terbinafine
Antivirals	Nelfinavir, lamivudine, nevirapine
Antiprotozoal	Mefloquine
Antiulcer drugs	Ranitidine, omeprazole, famotidine
Endocrine system	Bisphosphonates
Cardiovascular	Metoprolol, losartan, valsartan
Anticoagulants and antiplatelets	Low molecular weight heparin, dipyridamole
Fibrinolytic drugs	Alteplase
CNS drugs	Fluoxetine, sumatriptan, bupropion
Cytotoxic	Taxanes, cisplatin, bleomycin, dacarbazine, methotrexate
Vaccines	Hepatitis B
Photoactive substances	Methoxsalen (8-methoxypsoralen)

Drug Induced Serum Sickness-like Reaction (DI-SSLR)

This reaction pattern is characterized by a clinical triad of fever, skin rash and arthralgia/arthritis. It is called so because of its similarity to the reaction induced by serum sickness which was noted with horse serum injections given in the past. Classical serum sickness is a type III hypersensitivity reaction to foreign proteins that result in immune complex deposition within blood vessels of various organ systems that include skin, joint and other systems. However drug induced SSLR, which is the most common cause of SSLR, does not show demonstrable circulating immune complexes in vessels though clinical presentations are similar. The disease is reported often with beta-lactams especially, cefaclor and amoxicillin. The incidence is reported to be higher with cefaclor in children in the UK, probably due to higher usage of cefaclor.[39]

The pathophysiology of DI-SSLR is not clear. Impaired drug metabolism and production of reactive intermediates were considered to be causes in *in vitro* studies. The lack of cross reactivity with other cephalosporins and the lack of immune complexes make it unlikely to be a hypersensitivity reaction.

Histopathology shows dermal edema, superficial and deep perivascular inflammatory infiltrate of neutrophils, lymphocytes and eosinophils. Vasculitis is usually absent.

The common drugs causing this reaction are listed in the Table 21.3.

Table 21.3: Some common drugs causing drug induced serum sickness like reaction (DI-SSLR)[39]

Antimicrobials	**CNS drugs**
• Cefaclor and other cephalosporins	• Bupropion
• Penicillins and other β-lactams	• Fluoxetine
• Meropenem	**Cardiac**
• Minocycline	• Clopidogrel
• Co-trimoxazole	• Streptokinase
• Rifampicin	**Biologics**
• Itraconazole	• Infliximab
• Griseofulvin	• Rituximab
	• Omalizumab

The latency period is usually 7 days with a range of 1-13 days.

Clinically, lesions present as pruritic urticarial wheals which may be migratory. The lesions may be florid in their presentation, seen as purpuric or bullous eruptions. Facial edema is often an

accompanying presentation. Mucosal lesions are most often absent. Morbilliform, urticarial, bullous and purpuric variants are known to occur. Joint pains and swellings are frequently encountered and often affect the small joints of the hands and feet. Renal and hepatic involvement are rare compared to classical serum sickness.

Urticarial vasculitis, Still disease, Schnitzler syndrome, human parvovirus B19 infection, Kawasaki disease and hereditary autoinflammatory diseases are differentials of the clinical presentation.

Drug withdrawal results in improvement of rash and musculoskeletal symptoms with a median duration of 5 and 3 days respectively. While skin tests like patch tests and intradermal tests are negative, oral provocation is relatively safe and can confirm the diagnosis.

Treatment involves use of antihistamines, antipyretics and systemic steroids if necessary.

Drug Induced Contact Urticaria

Contact urticaria is defined as immediate or near-immediate whealing and itching occurring at sites of penetration of skin or mucous membranes by the offending agent. The local reaction, consisting of redness, edema and pruritus, is short lived, fading within an hour provided that the offending substance is completely removed. Contact urticaria is classically represented by stinging nettles (Urtica dioica) and is also caused by a variety of compounds, such as foods, preservatives, fragrances, plant and animal products, metals, and rubber latex. It needs to be distinguished from contact physical urticarias in which the skin reacts to direct contact with a physical stimulus (cold, pressure, sunlight, etc.).

Drugs can rarely cause contact urticarial reactions. The list of drugs causing contact urticaria is shown in Table 21.1 Drug induced contact urticaria can be allergic (estrogen, progesterone, penicillin, gentamicin, neomycin, bacitracin, promethazine) or pseudo-allergic (menthol, polyethylene glycol, cetyl stearyl alcohol). Atopic subjects are considered more likely to develop drug aggravated contact urticaria due to allergic pathomechanisms.[27]

Urticarial Vasculitis

Urticarial vasculitis is a rare form of chronic urticaria in which patients present with urticaria like lesions (Fig. 21.3 A and B) but they are painful and usually last more than 24 hours. The diagnosis is clinched by the histological evidence of vascular damage on a skin biopsy. These patients may have associated systemic symptoms, including evidence of multisystem involvement due to circulating immune complexes. Purpura, pigmentation, pain and tenderness is often an accompaniment of this reaction and this should alert the physician to the possibility and prompt a skin biopsy for histological examination. However, it is important to appreciate that in most cases of urticarial vasculitis due to a drug or another cause, the rash is clinically indistinguishable from chronic urticaria. A thorough workup for evidence of renal, cardiovascular, pulmonary and neurological involvement is necessary.

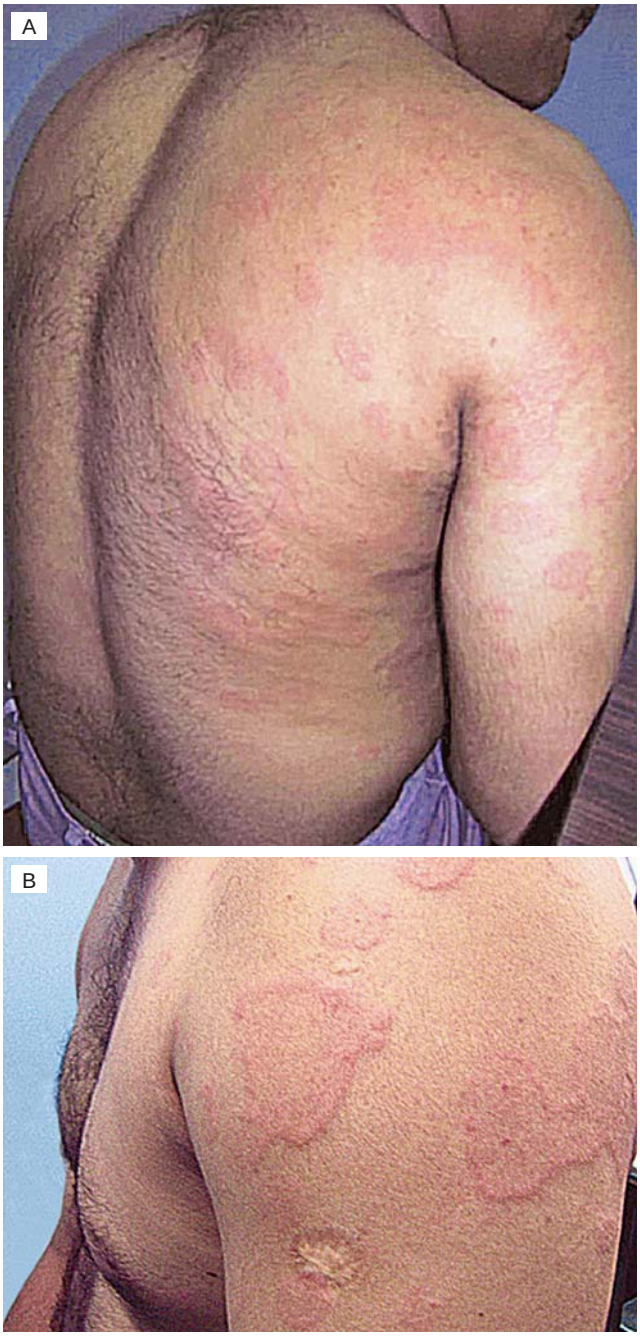

Fig. 21.3: (A & B) Wheals in urticarial vasculitis. The lesions in contrast to urticaria usually last longer, may be painful and heal with pigmentary changes upon resolution.

Drug-induced urticarial vasculitis is fortunately rare. ACE inhibitors, penicillin, sulfonamides, fluoxetine, cimetidine, diltiazem, thiazides, potassium iodide, non-steroid inflammatory drugs, and glatiramer acetate are drugs known to cause urticarial vasculitis.[27]

APPROACH TO THE PATIENT WITH DRUG INDUCED URTICARIA/ANGIOEDEMA

Clinical Evaluation

When the clinician is encountered with an urticarial or angioedematous eruption it is essential to take a detailed history to identify if the rash is secondary to drug intake. The onset of reaction after intake of a specific drug, its temporal association, stoppage of reaction on withdrawal, a past history of similar reaction and exclusion of infections or other causes as cause of urticaria or angioedema are important steps in determining whether the reaction is truly drug induced. Very often, there are multiple drugs in a patient's drug chart and it is not possible to identify a culprit drug. When the rash has occurred concurrently with an infection, it is difficult to pinpoint whether the rash is drug induced or infection induced. Also, groups of drugs may cross react when one drug in a group is administered as an alternative to the other. e.g. aromatic anticonvulsants (phenytoin, carbamazepine and phenobarbitone) analgesics (asprin and NSAIDs) and antibiotics (penicillin and cephalosporins share a beta lactam ring).

Lab Investigations

Eosinophilia and raised serum total IgE levels are simple tests that help to arrive at a probable diagnosis of a drug induced rash. However, these are non specific.

Tryptase measurements are most useful in the laboratory confirmation and diagnosis of anaphylaxis, for example in a patient who develops shock intraoperatively. Tryptase is a tryptic neutral protease present only in human mast cells and in very small amounts (500-fold less) in basophils. Tryptase release from cells parallels histamine release, and is a marker of mast cell activation. Serum tryptase levels increase greatly after anaphylactic shock and anaphylaxis, but are negative in anaphylactoid non IgE mediated reactions. Serial measurements may be needed to confirm mast cell participation in milder reactions.[2,37]

Role of Skin Testing

Prick tests, intradermal tests and patch tests have been tried to elicit urticarial eruptions. However, it may not be possible to do this in patients with dermographism and in the subset of patients who need to continually use specific drugs (as drugs need to be stopped prior to skin tests). Penicillin reactions are classically diagnosed in the clinic by skin testing. They are often caused not by penicillin itself but to its metabolic products. Allergy may be to known or unknown drug metabolites and its hapten. Skin testing for penicillin has been well standardized and is described elsewhere.[30,31] It is performed using benzyl penicilloyl polylysine (PPL) which is available commercially and a minor determinant mixture (MDM) which is a variably formulated mixture of penicillin and its metabolic products (e.g. crystalline benzylpenicillin, benzylpenicilloate, and benzylpenilloate). The addition of amoxicillin and ampicillin may improve the yield of positive reactions. Skin testing may be negative if performed soon after a reaction or if there is a long interval between reaction and testing.[32]

A study was done by Barbaud et al. in patients with urticaria and angioedema to examine the usefulness of skin testing in drug allergy, in general. Patients were first patch tested. If the result was negative they were then prick tested and if this was negative intradermal tests were carried out. Patch testing was positive in 11% of patients, prick tests were positive in 29% and intradermal testing positive in 50%. Prick, intradermal, and patch tests together were positive in 67% of patients.[33]

Oral Provocation Tests

Rechallenge with the suspected drug is confirmatory, but may be challenging to the physician and ethically questionable, as urticaria and angioedema may progress to anaphylaxis on resensitization and is potentially life threatening. They are the best way to prove non IgE mediated anaphylactoid reactions. It is to be considered only in those cases where the benefit of testing outweighs the risk of anaphylaxis. They should only be carried out in patients who have not had life-threatening reactions and where in vitro testing and skin testing is negative. Testing with a placebo is also recommended.[34,35]

In Vitro Testing

This is done in those patients in whom skin testing cannot be performed. It is non invasive and hence does not carry the risk of prick testing or intradermal testing or oral provocation testing. In pseudoallergic, non IgE mediated anaphylactoid reactions, skin tests and antibody tests are negative, by definition. Tests include serum total IgE, drug specific IgE (RAST), histamine release assays

and serum tryptase measurements. Specific IgE tests exist are available for benzylpenicillin (penicillin G), phenoxymethylpenicillin (penicillin V), ampicillin, amoxicillin, gelatin, corticotropin (adrenocorticotrophic hormone) and insulin (porcine, bovine, and human)[36] Further information regarding in vitro testing is detailed in the chapters on skin testing and patch testing (Chapters 9 and 10).

TREATMENT OF DRUG INDUCED URTICARIA AND ANGIOEDEMA

Patients presenting with urticaria of mild to moderate variety should be managed with oral antihistaminesfexofenadine, loratadine, cetirizine, levocetirizine, ebastine, mizolastine are often used to control the attacks.

In severe attacks, parenteral antihistamine may be required and may be administered intramuscularly or intravenously. The use of H2 antihistamines is of debatable value. Systemic corticosteroid may be required when there are evidences to suggest systemic involvement like dyspnea, hypotension, shock, urticarial vasculitis or serum sickness like reaction. Adrenaline administered subcutaneously is very effective when an IgE mediated hypersensitivity is suspected strongly as adrenaline is a physiologic antagonist of histamine. Adrenaline is also effective when there is direct mast cell release by drugs such as anaesthetics, codeine or radiocontrast media.

Patients may occasionally progress to anaphylaxis if urticaria or angioedema is untreated. Acute anaphylaxis can be recognized by urticaria, angioedema, dyspnea and hypotension. The condition is potentially life threatening and interventions need to be done early to prevent progression. Interventions for management of anaphylaxis and anaphylactoid reactions are dealt in detail in the subsequent chapter (Chapter 29).

Box 21.2 summarizes the interventions for management of drug induced urticaria, angioedema and anaphylaxis proposed by one of the authors (author 2). The protocol for severe reactions has been adapted from British Guidelines.[38]

DRUG INDUCED PRURITUS

Pruritus is an unpleasant sensation that evokes the desire to scratch. Drug induced pruritus often presents without a skin rash (Fig. 21.4). This may clinically present as generalized or localized pruritus.[40] It may be acute (lasting only days) or chronic (longer duration lasting weeks or months). The onset may

Box 21.2: A proposed model for clinical interventions for urticaria and angioedema

- *Stop offending drug*
- *Mild to moderate urticaria/regional angioedema*
  - Start one of these oral antihistamines (Fexofenadine 120 mg/180 mg, Loratadine 10 mg, Cetirizine 10 mg, Levocetirizine 5 mg, Ebastine 10 mg.

    Hydroxyzine 10/25 mg, Promethazine 10/25 mg, Pheniramine maleate 25 mg, Chlorpheniramine maleate, Dexchlorpheniramine maleate 2 mg are the other options).
  - Oral steroids may rarely be needed if no response to above (prednisolone 5 mg/10 mg, methylprednisolone 4 mg/8 mg, Deflazacort 6 mg/12 mg are options).
- *If severe urticaria/generalized angioedema/urticarial vasculitis/serum sickness like reaction*
  1. Antihistamines
     - Pheniramine maleate 25 mg, Promethazine 25 mg, Hydroxyzine hydrochloride 25 mg.
  2. Parenteral adrenaline
     - Indications: Administered if due to type IgE mediated sensitivity or mast cell mediator release.
     - Dose: 0.5 cc, subcutaneously slowly over 3-5 minutes.
     - Preferably injected with an insulin syringe with 26G needle to gain better control while pushing the drug.
     - May need repeated doses
  3. Oral or parenteral steroids
     - Hydrocortisone 100 mg iv
     - Betamethasone/dexamethasone 1 mL (4 mg)
- *If patient progresses from generalised urticaria/angioedema to anaphylaxis/presents de novo as anaphylaxis (Stridor, wheeze, respiratory distress or clinical signs of shock)*
  1. Positioning:
     - Foot end elevation and supine position if in hypotension, Sitting up if breathless
  2. Monitor BP pulse and respiration
  3. Airway, breathing and circulation check
  4. Initiate oxygen high flow (10-15 L/minute)
  5. Adrenaline: Subcutaneous epinephrine (adrenaline) 1 in 1000 solution, 0.5 mL

     Repeat in 5 minutes if no clinical improvement
  6. Antihistamine:
     - Chlorpheniramine 10-20 mg,
     - Promethazine/pheniramine 25 mg 0.5-1.0 mL IM or slow IV

(Continued...)

Box 21.2: A proposed model for clinical interventions for urticaria and angioedema (Continued)

7. Corticosteroids:
   - For all severe or recurrent reactions and patients with asthma
   - Hydrocortisone 100-500 mg IM/or slow IV
8. IV fluids:

   If clinical manifestations of shock do not respond to drug treatment 1-2L IV fluid may be given. Rapid infusion or one repeat dose may be necessary.

Warnings

1. Patients should be warned of the possibility of an early relapse and kept under observation for 8 to 24 hours, particularly if the patient has asthma, a history of biphasic response or may continue to absorb the drug.
2. An inhaled β2-agonist such as albuterol (salbutamol) may be used as an adjunctive measure if bronchospasm is severe and does not respond rapidly to other treatment.
3. If profound shock is judged immediately life-threatening give cardiopulmonary resuscitation/ advanced life support if necessary.
4. Slow IV epinephrine 1:10000 solution. This is hazardous and is recommended only for an experienced practitioner who can also obtain IV access without delay. **Note the different strength of epinephrine that is required for IV use.**
5. A crystalloid may be safer to use than a colloid.
6. β-Blockers may increase the severity of an anaphylactic reaction and antagonize the response to epinephrine.

IM - intramuscular; IV - intravenous.

be with the first dose of the drug or may be delayed in time. Acute onset of drug induced pruritus starts early and resolves early on withdrawal of the drug. Delayed onset is often seen with liver dysfunction or cholestasis wherein the pruritus occurs several weeks after the start of treatment[34,41] barring exceptions where it has occurred at shorter intervals.[35] The resolution of pruritus may be within a short duration or may persist for several months or years post withdrawal.[40]

The incidence and clinical presentations of drug induced pruritus have not been well characterized as there are few studies conducted. Studies have been conducted only with opioids, hydroxyethyl starch and vancomycin. However case reports have been reported often with specific drugs in literature.[39] In one large epidemiological study it has been shown that, among hospitalized patients, pruritus without concomitant skin

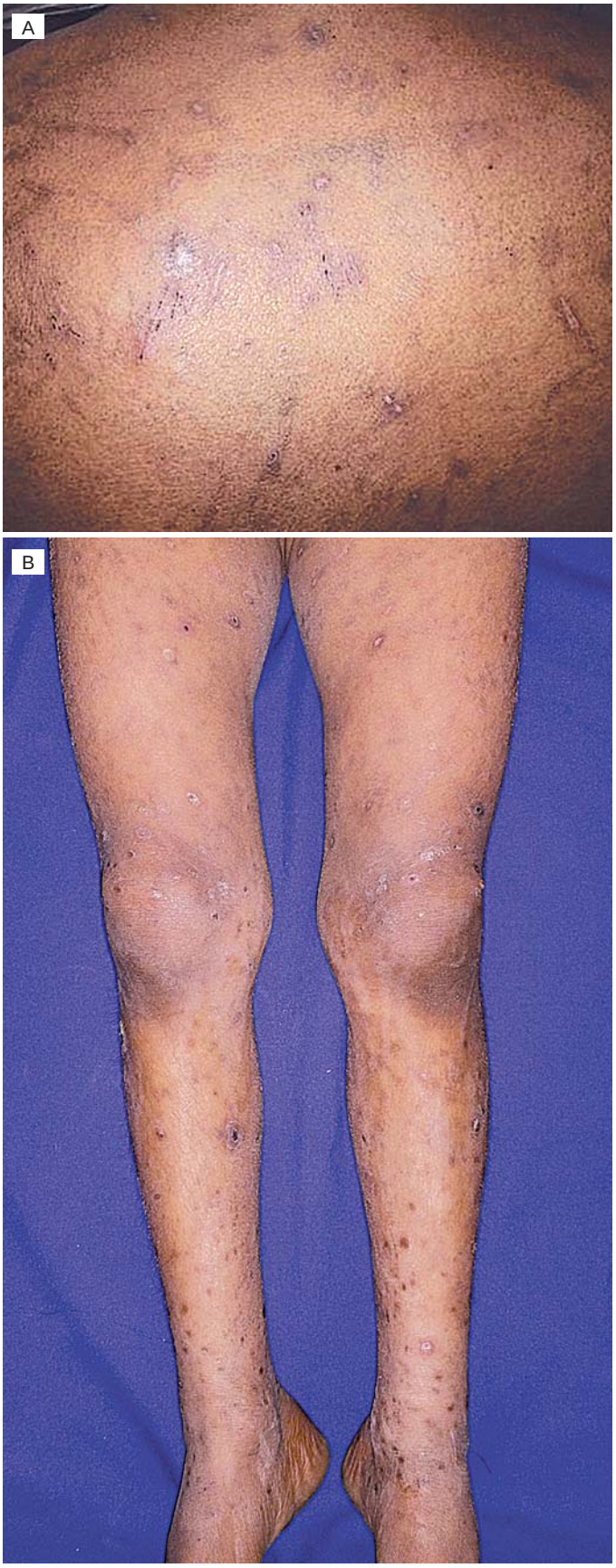

Fig. 21.4: Drug induced pruritus on trunk (A) and lower limbs (B) due to chloroquine. Generalised pruritus and excoriations without any other rashes may be a presentation of CADR.

lesions accounted for approximately 5% of adverse reactions after drug intake. Drug induced cholestasis or hepatotoxicity leading onto pruritus is a common presentation. It has been reported with several drugs including tetracycline, methimazole, metformin, verapamil, erythromycin, penicillins, candesartan, amlodipine, amitriptyline, ticlopidine, oral contraceptives, anabolic steroids and sodium valproate.[41-51] It is very difficult also to establish whether the pruritus is a 'primary drug induced pruritus' or pruritus as a symptom of other drug induced morphologic patterns like urticarial or lichenoid eruption.

PATHOGENESIS OF DRUG INDUCED PRURITUS

The pathogenesis of pruritus is variable and co-morbidities like hepatic or biliary disease, cholestasis, renal disease, neurologic disease, elderly, xerotic skin are important precipitating factors.[54] pharmacogenomics profile (e.g. enzyme deficiencies like G6PD in chloroquine induced pruritus) and phototoxicity (e.g. 8-methoxypsoralen) may also predispose the individual to drug induced pruritus. Very often the cause is not known. The pathomechanisms of drug induced pruritus have been elucidated by Weisshaar et al.[44] This has been modified to include several additional pathogenetic mechanisms and summarized in the table below (Table 21.4).

The list of drugs causing pruritus is exhaustive. The most common drugs are mentioned in the Table 21.4.

TYPES OF DRUG INDUCED PRURITUS

They have been classified on the same lines as urticaria as acute and chronic pruritus. Acute pruritus lasts less than 6 weeks whereas chronic pruritus lasts more than 6 weeks.[40]

While acute pruritus subsides early after the drug is withdrawn, chronic pruritus persists until the drug is eliminated slowly from the body, as occurs with Hydroxyethyl starch, a plasma expander. Chronic pruritus in HES induced pruritus can occur due to neuronal storage of the substance which degrades slowly over prolonged period of time.[66] Chronic pruritus can occur due to unknown mechanisms as well. Pruritus may be a presentation preceding a primary skin disease like urticarial or lichenoid eruption.

Pruritus usually occurs after intake of systemic drugs but may be noted after topical application of drugs like ciprofloxacin ointment, neomycin application or calcineurin inhibitors like tacrolimus and pimecrolimus. Topical preparation of Diphenhydramine (CALADRYL) has also been noted to induce pruritus (author's experience).

Acute Pruritus

Several drugs can cause acute pruritus and the list is exhaustive and beyond the scope of this chapter. However the well-studied models for acute pruritus are chloroquine, serotonin reuptake inhibitors (SRIs) and opioid induced pruritus. Their features are summarized in the Table 21.5.

Table 21.4: Proposed pathomechanisms drug induced pruritus (modified from Weisshaar et al.)[44]

	Pathomechanism	Drugs
1.	Cholestasis	Antibiotics-Penicillin, Minocycline, Trimethoprim-sulfamethoxazole, Carbapenems Cardiac-ACE inhibitors, Sildenafil, Amiodarone, Fractionated heparins, Ticlopidine, Antidiabetic-Biguanides, Sodium valproate, Oral contraceptives, Methimazole
2	Hepatotoxicity	Sex hormones-Oral Contraceptives, Oestrogen Supplements, Anabolic Steroids, Erythromycin, Phenothiazine, Azathioprine, Penicillamine
3.	Xerosis	Lipid lowering agents, Retinoids, Tamoxifen
4.	Phototoxicity	8- methoxy psoralen
5.	Neurologic	Tramadol, codeine, cocaine, morphine, fentanyl (Centrally mediated via μ receptors)
6.	Drug deposition	Hydroxyethyl starch (HES) deposits in small peripheral nerves or schwann cells of cutaneous nerves)
7.	Kinin metabolism	ACE Inhibitors (increased bradykinin levels)
8.	Eicosanoid metabolism	NSAIDs (mediated through excess of leukotrienes)
9.	Cytokine mediated	Interleukin-2 (direct pruritogenic effect of IL-2)
10.	Genetic background	Antimalarials- Chloroquine (60-70% of Africans;less in Caucasians and Asians)
11.	Idiopathic	Gold, Lithium, Methyldopa, Rifampicin, Metronidazole, GM-CSF, Lapatinib

Table 21.5: Features of drug induced pruritus

Chloroquine induced pruritus[55-58]	SRI induced pruritus[62,63]	Opioid induced pruritus
• Noted more in Africans races (60-70%) than Caucasians and Asians • Young adults (<40 years of age) • Pruritus is higher in G-6PD deficient individuals whereas it is lower in sickle cell trait individuals • Also noted with other antimalarials (amodiaquine, halofantrine, hydroxy-chloroquine)[49,50] • Onset within 24 hours; last longer than 48 hours in 50% • Pruritus may be localised to hands and feet or may be generalized. • Aquagenic or post wetness pruritus is often seen mainly lower extremities and back, after hot showers, begins within minutes of water contact, reaches peak over several minutes and remains at low intensity for several hours[51] • Can be a cause for non compliance to antimalarials • Severity of pruritus correlates with malarial parasite density[45] • Proposed mechanisms for pruritus include 1. Histamine release by chloroquine 2. Slower metabolism of chloroquine 3. Endogenous opioids produced via μ receptors induce pruritus	• Can induce pruritus though it is also used for management of severe pruritus to counter centrally mediated factors. • Possibly related to increased serotonin concentrations in the periphery • SRIs taken with serotonin inducers/precursors/alkaloids like chocolates are more likely to induce pruritus • Effect is dose dependent	• Used for treatment of acute and chronic pain • Pruritus depends on type of opioid used and mode of use (intrathecal morphine>epidural> intraspinal>oral) • Parturients are a susceptible group • Facial areas more affected (as there is high concentration of opioid receptors in the area innervated by trigeminal nerve) • Centrally mediated pruritus via μ opioid receptors

Chronic Pruritus

Chronic pruritus that exceeds 6 weeks is best studied in the case of Hydroxyethyl starch (HES) infusion, a colloid used for fluid management in ICUs. Coagulopathy, bleeding, anaphylactoid reactions and pruritus are the recognized adverse effects of the drug.[40] Pruritus was first recognized as an adverse reaction in the early 1980s.[44] Later it was noted as a consequence of therapy given in otorhinology patients.[68] Subsequently several reports came in the 1990s.[67,68] The frequency of HES induced pruritus in literature has varied from 12.6% to 54%.[40] Pruritus can occur with small volumes but larger volumes lead to higher frequency and severe pruritus.

The features of HES induced pruritus are summarized in the box 21.3.

Box 21.3: Features of hydroxy ethyl starch (HES) induced chronic pruritus

- Onset: 3-6 weeks after HES infusion
- Duration: 4 weeks to 18 months; median of 10 months
- Triggers: Friction, bathing in warm water, physical stress
- Intensity: usually severe pruritus
- Consequences: Sleep disturbances, anxiety, impaired quality of life, suicidal ideation
- **Patho-mechanisms:**
  1. Deposits of HES were found in cutaneous nerves (Schwann cells, perineuronal cells, endoneural macrophages). HES is probably stored in neurons and leads to direct activation of pruritogenic nerves.
  2. HES deposits have also been seen in dermal macrophages, endothelial cells of blood and lymph vessels, and in some keratinocytes and Langerhans' cell raising a possibility that these cells may partake in provoking pruritus or exert a direct effect on sensory nerve fibres.
- Treatment: Difficult to treat; Naltrexone and phototherapy tried with minimal benefits

TREATMENT OF DRUG INDUCED PRURITUS

The diagnosis of drug induced pruritus is targeted to the suspected pathogenic mechanism. The options are stratified and summarized in Table 21.6.

Table 21.6: Proposed treatment of drug induced pruritus (based on Reich et al)[40]

Drug	First line	Second line	Third line
Chloroquine induced pruritus	Antihistamines (promethazine, chlorpromazine)	Naltrexone	Prednisolone, niacin
Opioid induced	Naloxone, Naltrexone (μ receptor antagonist) or nalbuphine (μ receptor antagonist and κ receptor partial agonist)	Droperidol and alizapride (dopamine D2 receptor antagonist)	Ondansetron and dolasetron ($5HT_3$ antagonist) Promethazine, diphenhydramine (sedative antihistamines)
HES induced	Naltrexone	Phototherapy	Capsaicin topically (poorly tolerated)
Cholestatic/hepatic pruritus	Ursodeoxycholic acid rifampicin	Cholestyramine	Naloxone, naltrexone, sertraline
Other types of Drug induced pruritus	Antihistamines (high dose)	μ receptor antagonists	Gabapentin, paroxetine, amitriptyline

LEARNING ESSENTIALS

- Urticaria, angioedema and pruritus without rash are important clinical presentations of drug rash.
- Drug induced urticaria and angioedema can occur due to immunologic and non immunologic causes.
- Immunologic causes can be IgE mediated, immune complex mediated or drug hypersensitivity related. Non immune causes include mast cell degranulation and alterations in kinin and arachidonic acid metabolism.
- Drug induced contact urticaria and urticarial vasculitis are immune reactions that mimic regular urticaria and angioedema.
- Anaphylaxis is a life threatening complication of generalized urticaria and angioedema if untreated.
- Early recognition of the rash as being drug induced and prompt withdrawal of the drug arrests progression to anaphylaxis.
- Drug induced pruritus is a distinct entity often unrecognized. It presents as acute pruritus (lasts less than 6 weeks) and chronic pruritus (lasts more than 6 weeks). The former is well studied with drugs like chloroquine, serotonin reuptake inhibitors and opioid antagonists whereas the latter is represented by hydroxyethyl starch (HES) induced pruritus.

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Chapter

22

Cutaneous Adverse Drug Reactions and the Hair

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SUMMARY

Drugs can affect the hair in many ways. The commonest manifestation of adverse drug reactions affecting the hair is in the form of hair loss. Other possible presentations include- increased hair growth, pigmentary changes or changes in the shape or texture of the hair. It is important for the dermatologist to be aware of these possible side-effects and link them to the causative drugs. This chapter reviews the common adverse drug reactions affecting the hair.

INTRODUCTION

Hair is an important target of adverse drug reactions. Systemic and topical medications may produce CADR which present with symptoms related to the hair. While hair loss (alopecia) is the most common presentation of hair related ADRs, it is difficult to conclusively correlate hair loss with a specific drug, as medical conditions may significantly overlap or confound the etiopathogenesis of alopecia. Alopecia is dependent on various factors like type of drug, dosage of drug and individual susceptibility.[1,2,3] Hypertrichosis and hirsutism, pigmentary alterations and altered hair texture and shape are other presentations of hair related CADRs.[4,5,6,7]

The commonest type of drug induced hair loss is reversible, diffuse, non-scarring alopecia, of which the commonest pattern is that corresponding to telogen effluvium.[1-4] The chapter describes some of the common reaction patterns induced by drugs.

DRUG INDUCED TELOGEN EFFLUVIUM

Drug induced telogen effluvium affecting the scalp hair (Fig. 22.1A) typically starts approximately 3 months after initiation of treatment. Associated trichodynia may be seen in some cases. Rarely body hair can also be affected. Drugs produce telogen effluvium through three main mechanisms.[1,2,3,4,8]

- Precipitation of follicles into premature telogen. This is the commonest mechanism. There is a long list of drugs, which have been reported to induce premature telogen. Common drugs include – anticoagulants like heparin and antiretroviral drugs.
- Discontinuation of drugs, which maintain the hair in anagen. An example is hair shedding after stoppage of topical minoxidil.
- Premature detachment of club hairs associated with shortening of normal telogen phase. This is classically seen with systemic retinoids.

Common Groups of Drugs Associated with Telogen Effluvium

Anticoagulants

Heparin and coumarin derivatives can both be associated with telogen effluvium (although the incidence is more common with heparin and heparinoids). Low molecular weight heparins like dalteparin and tinzaparin have also been reported to cause patchy alopecia.[9-12] Although the exact mechanism of hair loss is not clear, telogen effluvium does appear to be the primary pattern of hair loss related to anticoagulants. It usually occurs in patients on a higher dose of anticoagulants. The newer Direct Oral Anticoagulants (DOAC) like rivaroxaban and dabigatran have also been reported to have hair loss as a side effect.[13]

Antimicrobials

The commonest drugs in this group associated with hair loss are anti-tuberculosis medicines and antiretrovirals. Isoniazid is the commonest

anti-tuberculosis drug associated with hair loss.[14,15] In the case of antiretrovirals, indinavir is the drug most commonly associated with reversible, diffuse alopecia. Indinavir can also cause patchy, alopecia areata- like hair loss. In general, combination antiretroviral therapy is more likely to be associated with severe hair loss.[1,2,16]

Fig. 22.1: Drug induced telogen effluvium in a middle aged female on anti psychotic medication olanzapine (A) and due to fluoxetine (B).

Cardiovascular Drugs

Beta-blockers – mainly propranolol and metoprolol have been associated with telogen effluvium. ACE inhibitors like captopril and antiarrythmics like amiodarone can also cause diffuse reversible hair loss.[2]

Psychiatric and Neurological Medications

Antidepressants like fluoxetine (Fig. 22.1B) can cause diffuse hair loss, which may sometimes have a delayed onset. Tricyclic antidepressants and lithium have also been reported to cause telogen effluvium. It is important to check for thyroid function in patients on lithium as it can be associated with hypothyroidism, which by itself can lead to telogen effluvium.[1,2] Valproic acid can cause dose-dependent telogen effluvium.[17] Dopaminergic therapy in Parkinson's disease with levodopa has been associated with telogen effluvium, more commonly in females.[1,2]

Retinoids

Retinoids can be associated with dose related telogen effluvium which can be quite severe but is usually reversible (Fig. 22.2). In addition, acitretin can also produce changes in hair color (repigmentation) and texture (kinking). Premature teloptosis (The process in which the club hair is shed from the follicle that is already occupied by a new terminal anagen hair) is considered the primary mechanism in retinoid related alopecia. Rarely body hair can also be involved.[1,2,18-21]

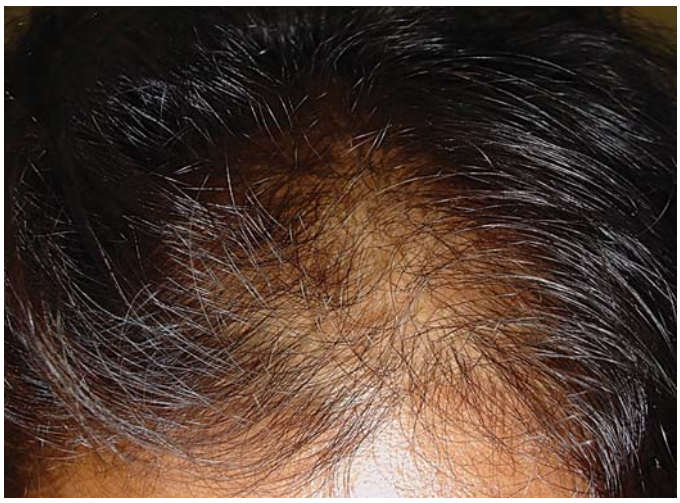

Fig. 22.2: Non scarring alopecia induced by isotretinoin in a patient of acne vulgaris; this usually reverses on stopping therapy. (Courtesy of Dr. Sandipan Dhar, Kolkata.)

Interferons

Non-dose dependent, reversible hair loss can be seen in upto 50% of patients on interferons. Localized alopecia at injection sites has also been reported. Hair straightening and whitening are other side effects of interferons.[1,22,23]

Immunomodulators and Immunosuppressants

Telogen effluvium has been reported with

tacrolimus, mycophenolate mofetil, leflunomide and tamoxifen.[1,24,25]

Other Drugs

As mentioned previously, many drugs have been reported to cause diffuse hair loss, although there is no clear, consistent evidence in some of these cases. These are shown in the Box 22.1.[1,2,26]

Box 22.1: Drugs reported to cause hair loss

Allopurinol
Amphetamines
NSAIDs (like ibuprofen, indomethacin, naproxen)
Antithyroid drugs (carbimazole, iodine, propylthiouracil)
Buspirone
Cholestyramine
Chloramphenicol
Cidofovir
Cimetidine
Clonazepam
Clotrimazole
Colchicine
Glibenclamide
Gold salts
G-CSF (granulocyte-colony stimulating factor)
Haloperidol
Hypocholesterolemic drugs (like clofibrate, fenofibrate)
Imiquimod
Metformin
Methazolamide
Mesalazine
Methysergide
Metyrapone
Nicotinic acid
Nitrofurantoin
Octreotide
Olanzapine
Pyridostigmine
Risperidone
Sulphasalazine
Terbinafine
Terfenadine
Trazodone
Triazoles (fluconazole, itraconazole)
Vasopressin

Management

The primary step is to stop the drug wherever possible. While taking the history it is important to identify a clear temporal relationship with all possible drugs which the patient is or was using (it has to be kept in mind that the hair loss usually starts 3-4 months after starting treatment). If a particular drug is suspected, it needs to be stopped for at least 3 months for assessment. Regrowth following withdrawal of the drug and recurrence of hair loss on re-exposure to it supports the diagnosis of drug induced telogen effluvium.[2,27] A detailed history will also help to exclude other causes of telogen effluvium. Wherever relevant, appropriate laboratory investigations need to be done to exclude endocrine, nutritional and autoimmune disorders.[28,29] It is also important to exclude other causes of diffuse non-scarring alopecia like androgenetic alopecia. Trichoscopy can be a useful tool in differentiating patterned hair loss/androgenetic alopecia from telogen effluvium.[30,31] The condition usually resolves spontaneously after stoppage of the drug. In some cases topical minoxidil may be useful. A proper evaluation of the patient is required to rule out an associated androgenetic alopecia. Minoxidil or finasteride might be required for improving the hair loss in these cases.[32]

DRUG INDUCED ANAGEN EFFLUVIUM

Anagen effluvium is usually associated with antineoplastic agents (Fig. 22.3 A) and immunosuppressives (Fig. 22.3 B). They possibly cause anagen hair loss by affecting rapidly multiplying cells like hair matrix. Rarely, other drugs or heavy metals can cause anagen effluvium (e.g. levodopa, colchicine, bismuth, boron, thallium and mercury).[34-37] The onset is sudden and the loss is severe. The hair loss is usually noticed 4 to 8 weeks after start of treatment. The anagen hair loss may be associated with a telogen effluvium. A typical finding is the constriction of the hair shafts (Pohl-Pinkus constrictions).[38] The severity of hair loss after chemotherapy (or radiation) depends on timing, dose, and duration of the treatment and synchronization of hair cycle.[39] The hair loss associated with chemotherapy (Table 22.1) also depends on the drug combination and the tendency to cause hair loss is variable depending on the drug.[1,40]

Management

Sudden onset of hair loss, a few weeks after starting chemotherapy strongly points towards a diagnosis of anagen effluvium. All the same, a detailed history and physical examination is essential to rule out other possibilities like telogen effluvium.

In anagen effluvium, only the proliferating cells in the bulb are affected, the stem cells of the bulge are spared, so hair loss is usually reversible. However, there is increased evidence that certain chemotherapy regimens can cause dose-dependent permanent alopecia.[40] The simplest strategy would be the use of wigs/hair-pieces along with appropriate counseling.[39] Scalp hypothermia and tourniquets can be preventive

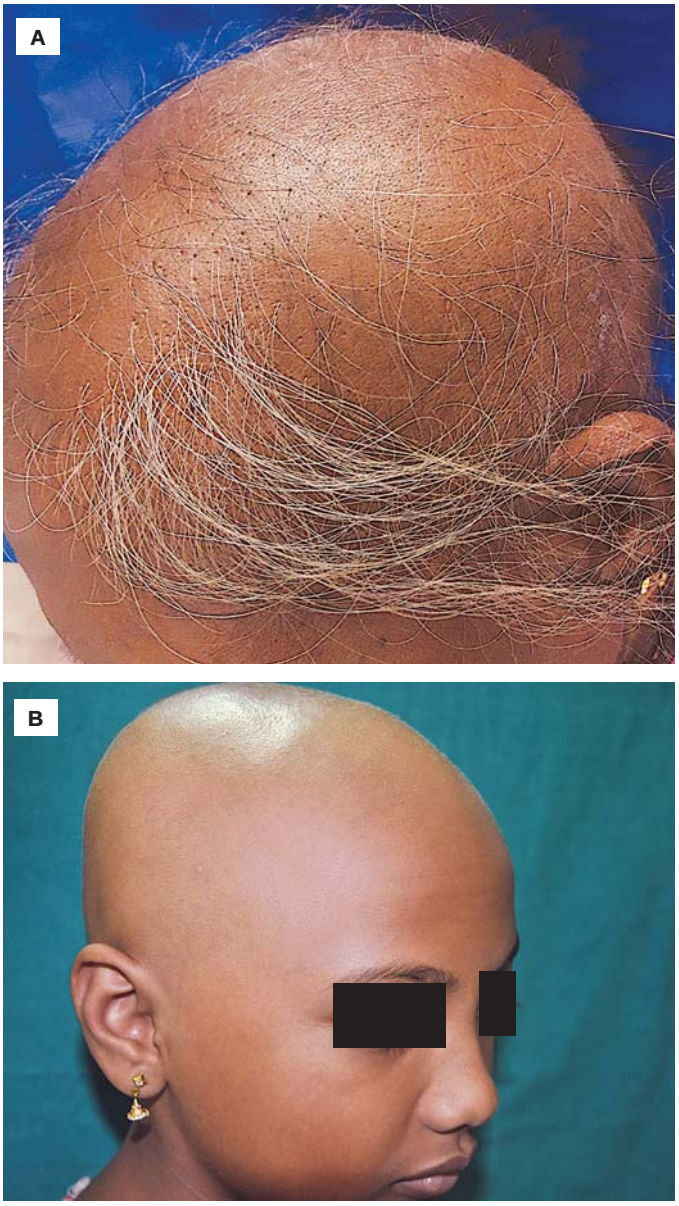

Fig. 22.3: (A) Chemotherapy induced alopecia – anagen effluvium in a young female induced by chemotherapy drugs in carcinoma breast; (B) Immunosuppressive induced alopecia- anagen effluvium in a child induced by cyclophosphamide therapy. (Courtesy of Dr. Sandipan Dhar, Kolkata.)

Table 22.1: Propensity of chemotherapy drugs to cause hair loss

Higher tendency	Lower tendency	Least tendency
Adriamycin	Bleomycin	Capecitabine
Cyclophosphamide	Busulfan	Carmustine
Daunorubicin	Cytarabine	Cisplatin
Docetaxel	5-fluorouracil	6-mercaptopurine
Epirubicin	Gemcitabine	Procarbazine
Etoposide	Mitomycin-C	
Ifosfamide	Melphalan	
Irinotecan	Vincristine	
Paclitaxel	Vinblastine	

to some extent. Scalp hypothermia (temperature less than 24°C) is postulated to work in two ways – by producing local vasoconstriction leading to reduced blood flow to the follicles in the period corresponding to the peak plasma concentration of the cytotoxic drug and also by reducing the biochemical activity of the hair follicle itself (which in turn makes it less susceptible to damage by the cytotoxic agent). Animal studies have suggested that various agents may reduce or prevent alopecia by protecting the hair bulb from the damaging effects of chemotherapy, but effectiveness has not been proven in humans. Topical minoxidil can be used to reduce the severity or shorten the duration of chemotherapy induced anagen effluvium.[1,41-46]

General hair care advice is also important. This includes avoidance of physical or chemical trauma. Shaving the head completely will help in easier use of prosthesis.[39,47]

DRUG INDUCED ANDROGENETIC ALOPECIA

Use of androgens (androgens as such may be used medically and some oral contraceptives may contain progestins with androgenic effects), anabolic steroids and DHEA (Dehydroepiandrosterone) containing vitamin supplements can all be associated with worsening or induction of androgenetic alopecia[2] (Fig. 22.4). Interruption of estrogen containing oral contraceptives (OCPs) can be associated with telogen effluvium. Gonadotropin-releasing hormone (GnRH) agonists like goserelin and triptorelin can also be associated with androgenetic alopecia. Non-steroidal aromatase inhibitors like letrozole have also been reported to cause androgenetic alopecia.[1,48,49,50]

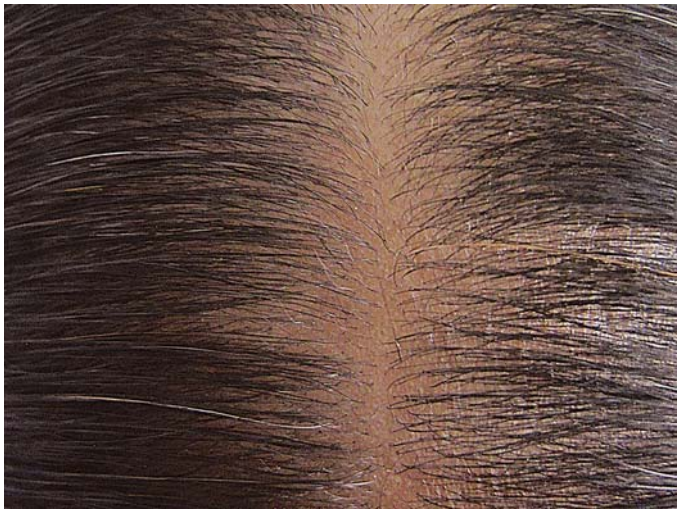

Fig. 22.4: Female pattern hair loss (FPHL) in a female taking oral contraceptive pills. Hormonal drugs like androgens, progestins, OCPs, and anabolic steroids can induce or unmask androgenetic alopecia as shown in the figure.

DRUG INDUCED SCARRING HAIR LOSS

Some drugs may induce scarring alopecia. Busulfan can produce permanent alopecia in upto 50% of patients.[51] ACE inhibitors, beta-blockers and TNF –alpha antagonists (including etanercept and infliximab) have been associated with drug induced lichen planopilaris, which in turn can lead to permanent, scarring alopecia.[1,2,52-54]

More recently, human epidermal receptor (HER) and epidermal growth factor receptor (EGFR) inhibitors have been implicated in drug induced scarring alopecia. This includes drugs like - Erlotinib and gefitinib (HER1 tyrosine kinase inhibitors), cetuximab, and panitumumab (which are monoclonal antibodies directed against EGFR) and Trastuzumab and pertuzumab (which are HER2 monoclonal antibody inhibitors).[55-58] Erlotinib and lapatinib have been associated with folliculitis decalvans and tufted hair folliculitis, which in turn can lead to scarring alopecia.[59,60]

HYPERTRICHOSIS AND HIRSUTISM

Both hypertrichosis and hirsutism can occur secondary to drugs. Hypertrichosis is excessive hair growth over and above the normal for the age, sex and race of an individual, in contrast to hirsutism, which is excess hair growth in women following a male distribution pattern. Hirsutism is usually associated with drugs having an androgenic effect like androgens and anabolic steroids. Other drugs associated with hirsutism include- ACTH, carbamazepine, danazol, and metyrapone.[1]

A large number of drugs, both topical and systemic, can induce hypertrichosis (Table 22.2). Topical minoxidil can be associated with hypertrichosis, especially when higher strength formulations are used.[5] Extensive hypertrichosis due to minoxidil has been reported in children and adults.[61] It has been suggested that some females may have hair follicles that are very sensitive to topical minoxidil and should use the lowest strength (2%) to help avoid unwanted hair growth. The hypertrichotic effect of minoxidil at sites other than the scalp is reversible and needs discontinuation of therapy.[62]

Topical prostaglandin analogs used for glaucoma like latanoprost, bimatoprost, and travoprost are associated with lengthening and darkening of eyelashes.[63] Hypertrichosis around a leg ulcer treated with prostaglandin E1 ointment has been described.[64] Topical, oral and inhaled steroids can also cause hypertrichosis, especially in children[65,66] (Figs. 22.5 A and B). Reversible hypertrichosis is a common and frequent side effect of systemic cyclosporine (Fig. 22.5 C). Topical calcineurin inhibitors like tacrolimus have also been reported to cause focal hypertrichosis.[67]

DRUG INDUCED CHANGES IN HAIR COLOR

Drug induced changes in hair color are relatively uncommon.[72,73] However, the dermatologist needs to think of this possibility in patients presenting with unexplained changes in hair color.

The most well documented drug induced

Table 22.2: Drugs reported to be associated with hypertrichosis[1,68-71]

Acetazolamide	Immunoglobulins	Radiotherapy
Albendazole	Indomethacin	Retinoids
Benoxaprofen	Interferons	Sodium tetradecyl sulfate
Beta-blockers (atenolol, betaxolol)	Infliximab[71]	Steroids (systemic and topical)
Calcium antagonists (nifedipine, verapamil)	Melphalan	Streptomycin
Cetuximab	Mercury	Tacrolimus
Cyclosporin	Methotrexate	Thallium
Desipramine	Methyldopa	Thiotepa
Diazoxide	Metyrapone	Tricyclic antidepressants (imipramine, maprotiline) Vasopressin, vinblastine Vincristine, zidovudine
Efalizumab[68]	Minoxidil	
Erlotinib[69]	Mitomycin	
Erythropoietin	Mitoxantrone	
Ethambutol	Nitrosoureas	
Ethionamide	Penicillamine	
Gefitinib[70]	Phenothiazines	
Gentamicin	Psoralens	
	Procarbazine	
	Prostaglandin analogs	

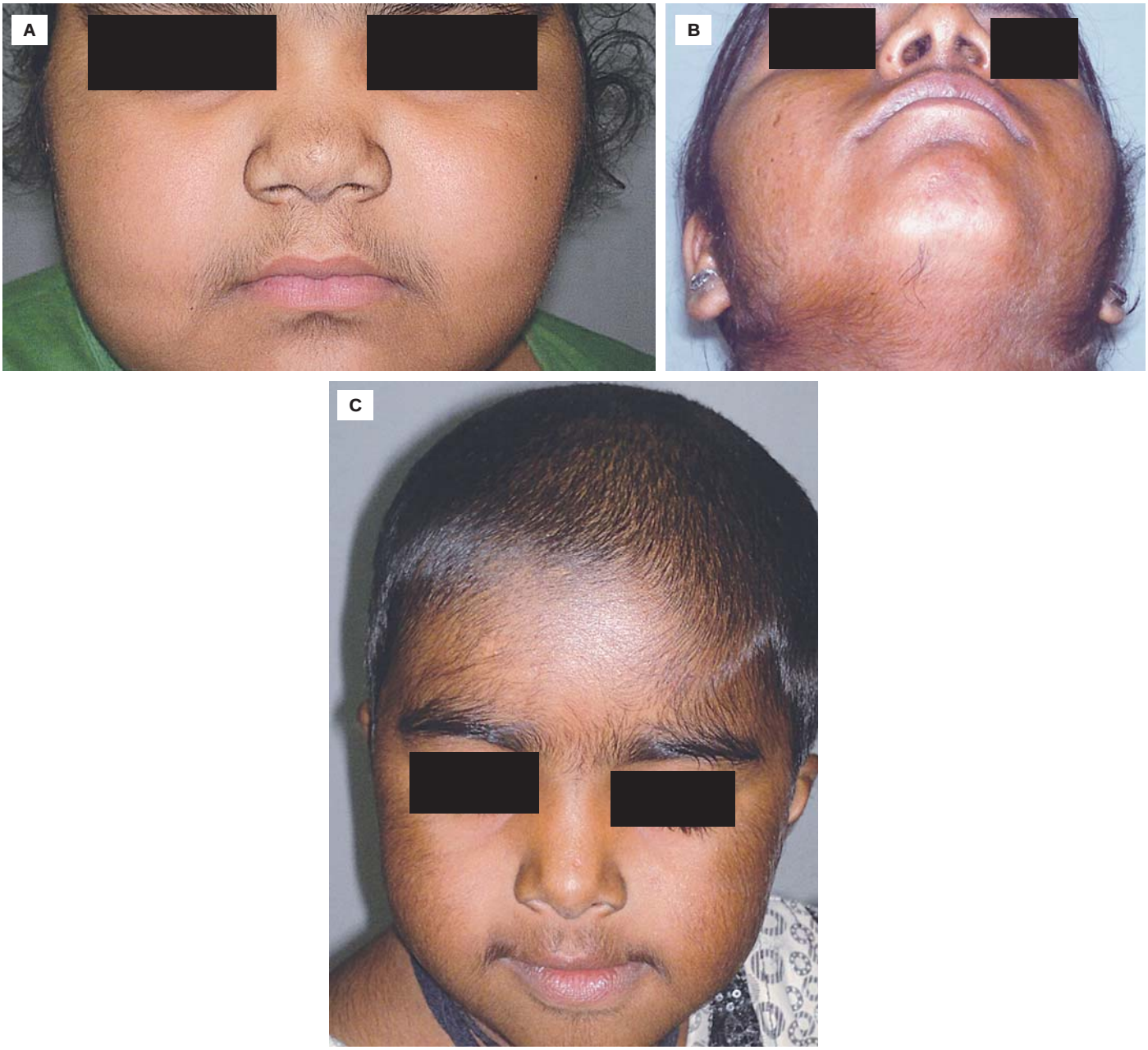

Fig. 22.5: (A) Hypertrichosis in a patient on long term immunosuppression with systemic steroid. Cushingoid facies may also be noticed; (B) Hypertrichosis in a patient due to topical steroid abuse on face. Topical steroid abuse is rampant in the Indian Subcontinent as "anti itch" or "fairness" creams; (C) Hypertrichosis in a patient on long term ciclosporin for nephrotic syndrome.

change in hair color is chloroquine-induced hypopigmentation. It is postulated that chloroquine inhibits pheomelanin synthesis and thereby mainly affects blond, light –brown and red-hair. It does not significantly affect eumelanin, so dark hair is usually not affected. The change can affect the eyebrows, eyelashes, axillary and pubic hair. Chloroquine induced hair bleaching is usually reversible.[73]

Cytotoxic drugs are associated with different types of color changes in the hair. Sometimes the color change may present with alternate dark and light bands (flag sign).[1] Cisplatin has been reported to cause both lightening and darkening of hair, while cyclophosphamide has been associated with darkening alone.[73] Vincristine has been reported to cause darkening and red discoloration of hair.[73] Patients on chemotherapy drugs, both traditional and targeted therapies, can developed greying of scalp hair, eyebrows and eyelashes (Fig. 22.6). Other drugs associated with hair color changes are mentioned in table 22.3.

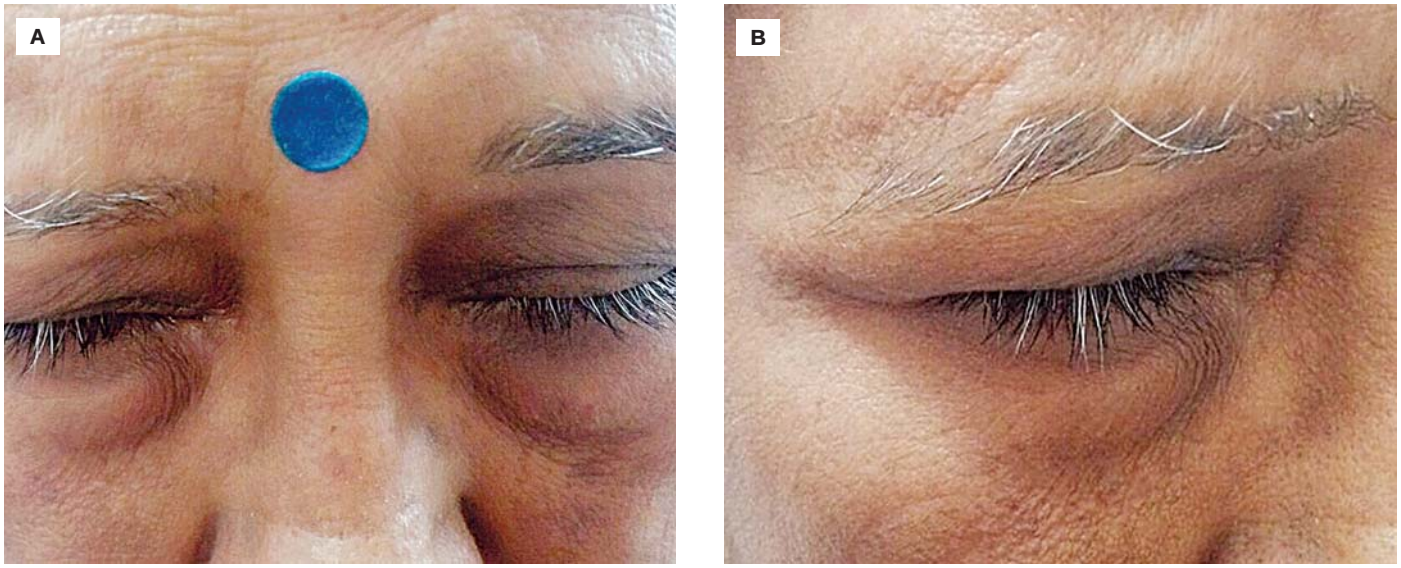

Fig. 22.6: (A) Greying of eyebrows and eyelashes in elderly female on chemotherapy for breast carcinoma, 2 months into the chemotherapy regime; (B) A close up view of the same patient.

Table 22.3: Drug induced hair color changes

Darkening	Lightening/graying	Other color changes
Indinavir[1]	Benzoyl peroxide[1]	Selenium sulfide (yellow discoloration)[7]
Bromocriptine[1]	Cyclosporine (poliosis)[1]	Dihydroxyacetone (yellow discoloration)[7]
Arsenic[1]	Hydroquinone[1]	Anthralin (yellow discoloration)[73]
Carbidopa/levodopa[1,74]	Interferon alpha[1]	
Minoxidil[1,73]	Phenols[1]	
Para-amino benzoic acid (PABA)[73]	Triparanol[1]	
Tamoxifen[1]	Valproic acid[73]	
Zidovudine[1]	Imatinib[76,77]	
Prostaglandin analogues	Sunitinib[78], dasatinib[79]	
Verapamil[73]	Heptaminol[80]	
Acitretin[19,20]	Paraphenylenediamine[81]	
Erlotinib[75]	Corticosteroids (inhaled)[82]	

TEXTURAL CHANGES IN HAIR INDUCED BY DRUGS

Drug induced structural changes are quite rare. Changes can include – straightening or curling/kinking of hair.

Straightening of hair has been reported with interferons and lithium. Curling and kinking of hair has been reported with cytotoxic/chemotherapy, indinavir, systemic retinoids, vemurafenib and valproic acid.[1,19,20,21,83]

EGFR inhibitors can cause trichomegaly in addition to kinking of hair.[84]

LOCALIZED HAIR LOSS ASSOCIATED WITH DERMATITIS

Localized hair loss in association with dermatitis can be secondary to chemicals like hydrogen peroxide and monoethanolamine, which can be part of hair dyes.[85]

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Chapter

23

Drug-Induced Pigmentary Alterations

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SUMMARY

Many drugs can cause pigmentary alteration in skin that may lead to a significant cosmetic concern with its significant psychosocial consequences. The pigmentary abnormality may involve skin alone or hair, nails, and mucosa may also be affected in varying proportion along with the skin. Drug-induced hyperpigmentation is seen more frequently than hypopigmentation. Some drugs that commonly cause hyperpigmentation include chemotherapeutic agents, antimalarials, heavy metals, psychotropic drugs, zidovudine, minocycline, clofazimine, amiodarone, and psoralens. Drug-induced hypopigmentary alteration of skin and hair is increasingly being reported with tyrosinase kinase inhibitors and newer targeted chemotherapeutic agents. Drug-induced dyspigmentation usually revert spontaneously after withdrawal of offending drug.

DRUG-INDUCED HYPERPIGMENTATION

Introduction

Of all the acquired pigmentation in skin, drugs are estimated to be responsible in approximately 20% of the cases. It can affect any age, sex, or race but tends to be more intense in darker skin as compared to the fairer. Although drug-induced pigmentary alteration do not cause significant morbidity, they can be cosmetically very disturbing to the patient. Chemotherapeutic agents, antimalarials, minocycline, amiodarone, zidovudine, heavy metals, and psychotropic medications are common cause of hyperpigmentation and will be discussed in details.

Pathophysiology

Multiple mechanisms are responsible for drug-induced pigmentation. Broadly speaking, they can be categorized as following:

- Direct deposition of the drug (or its drug metabolites) in the epidermis (e.g. arsenic combining with sulfhydryl group of epidermal cells) or dermis (e.g. heavy metal deposition in the dermis; phenothiazines, particularly chlorpromazine, react with melanin to form drug–pigment complexes).
- Post-inflammatory pigmentation (e.g., fixed drug eruption).
- Hyperproliferation of melanocytes or hyperproduction of melanin (e.g. oral contraceptive pills (OCPs)–induced pigmentation).
- Synthesis of some special pigments.

Some important drugs causing pigmentary changes and the patterns of pigmentation they cause are described below.

Chemotherapeutic Agents

Chemotherapeutic agents, mainly conventional ones have a propensity to cause hyperpigmentation which may be generalized or localized.[1] Adverse reaction manifesting as pigmentation results from oral, parenteral, or topical route. Table 23.2 summarizes a few anticancer drugs and patterns of hyperpigmentation caused by them. Linear flagellate erythema, a distinctive pattern of reaction known to occur classically with bleomycin may be seen with other drugs or conditions (Table 23.1).

Table 23.1: Causes of flagellate erythema/ pigmentation

Drugs	Diseases
Bleomycin	Hypereosinophilic syndrome
Bendamustine	Chikungunya fever
Docetaxel	Parvovirus B 19 infection
Peplomycin	Systemic lupus erythematosus
Trastuzumab	Dermatomyositis

Table 23.2: Chemotherapeutic agents–induced hyperpigmentation

Drug	Pathomechanism	Color	Extent	Distribution	Pattern	Mucosal involvement	Nail	Hair
Chemotherapeutic agents Taxanes[2] (Docetaxel, Paclitaxel)		Brown					+	
Topical carmustine		Brown	Localized					
Bleomycin[3]	Increased melanin in epidermis with scanty melanophages in dermis	Brown		Sites of scratching, joints, pressure	Flagellate hyperpigmentation (Figs. 23.1 A and B), sclerodermoid changes		+ Longitudinal melanonychia	
Busulfan	Inhibition of tyrosinase, increased melanin within basal keratinocytes and melanin within dermal macrophages	Brown	Generalized	Face, chest, forearms, abdomen	Resembles Addisonian pigmentation and porphyria cutanea tarda			
Cyclophosphamide		Brown	Generalized (Fig 23.2)	Palmoplantar				
Dactinomycin		Brown	Generalized	Face				
Daunorubicin		Brown		Photoexposed			+ Transverse melanonychia	
Doxorubicin	Increased melanocyte proliferation and epidermal melanin content	Brown to black	Generalized	Palmoplantar, small joints of hands		+	+	
5-FU[4,5]	Increased epidermal melanin	Brown		Photoexposed, dorsal hands, palmoplantar surfaces, and radiation ports	Supravenous serpentine			
Hydroxyurea		Brown	Localized or generalized	Back, sites of pressure				
Methotrexate		Brown		Photoexposed	Photo recall or UV recall reaction			+
Nitrogen mustard	Disaggregated melanosomes and increased melanocytes.	Brown	Localized					
Imatinib	Melanosome disaggregation inside keratinocytes	Brown				+	+ Diffuse melanonychia	+ Repigmentation of gray hair
Sorafenib, Sunitinib		Deep yellow	Diffuse					
Trastuzumab		Brown			Flagellate erythema			

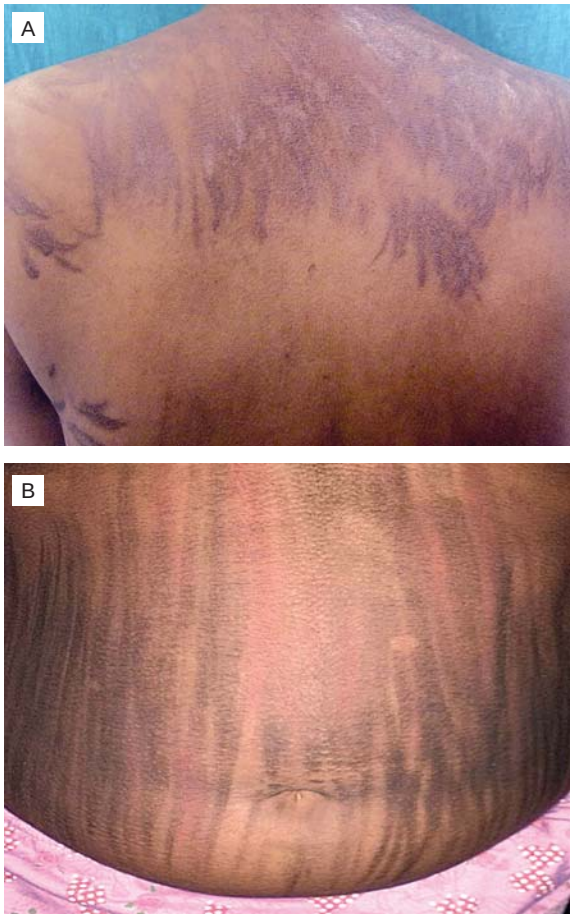

Fig. 23.1: (A) Striking flagellate pigmentation over back in a patient on bleomycin for testicular carcinoma. (Courtesy of Dr. Bela Shah, Ahmedabad.); (B) Linear and flagellate pigmentation on abdomen in a child on bleomycin. (Courtesy of Dr. Sandipan Dhar, Kolkata.)

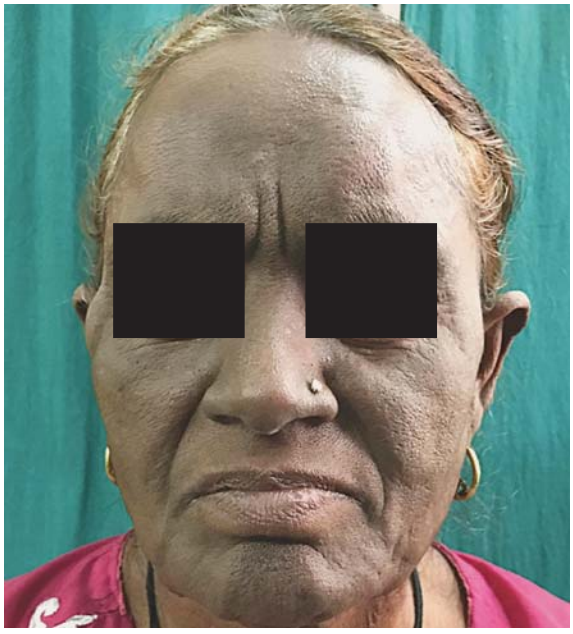

Fig. 23.2: Diffuse brownish black pigmentation in a patient of pemphigus vulgaris on dexamethasone cyclophosphamide pulse therapy.

Imatinib

A tyrosine kinase inhibitor (TKI) decreases melanocyte number, melanogenesis through suppression of tyrosinase and microphthalmia-associated transcription factor (MiTF), and inactivation of c-Kit signaling. Thus, hypo- or depigmentation is the main presentation (see later). This can also induce oral mucosal pigmentation involving hard palate and other areas, diffuse melanonychia, graying of hair, cutaneous hyperpigmentation frequently on face mimicking melasma.[7,8] Second-generation drugs of this group such as sunitinib, gefitinib, sorafenib, dasatinib,[9] and pazopanib can induce hypopigmentation.

Vandetanib

An anticancer drug that inhibits many different kinases such as epidermal growth factor receptor, vascular endothelial growth factor receptor, and the RET (rearranged during transfection) kinases and is used for treatment of medullary thyroid cancer and some other thyroid tumors. This can cause photosensitivity, blue dots, and skin pigmentation. Skin pigmentation induced by vandetanib has been successfully treated with 755-nm Q-switched alexandrite laser.[10]

Antivirals

Combination treatment with interferon α, both pegylated and nonpegylated (less common) along with ribavirin for hepatitis C infection is known to induce pigmentation of tongue (Fig. 23.3).[11] This is possibly mediated with melanin synthesis through induction of melanocyte-stimulating hormone (MSH). Same

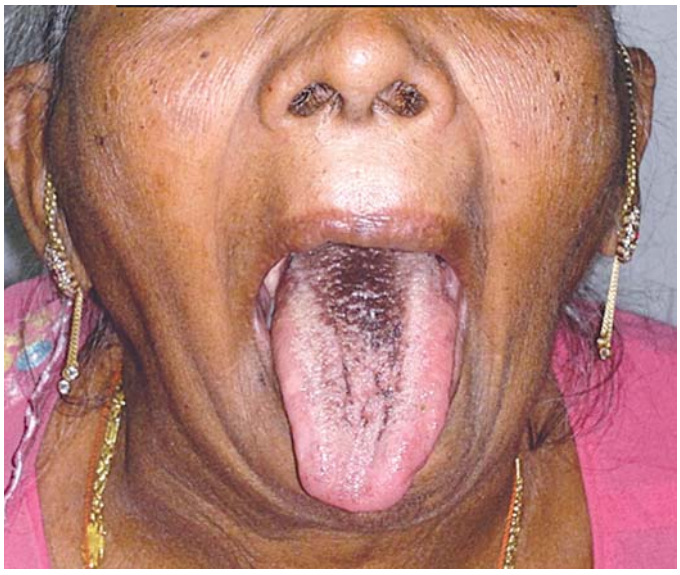

Fig. 23.3: Blackish discoloration of tongue seen in a patient on interferon α and ribavirin therapy for hepatitis C infection.

combination treatment for same indication has been reported to induce diffuse brown pigmentation of face.[12] Antiretroviral drugs (Table 23.3), particularly zidovudine is known to induce diffuse cutaneous hyperpigmentation accentuated in areas of friction, palm–soles, photoexposed skin, nail, and oral mucosal pigmentation (Fig. 23.4).[13–15] Histologically, both epidermal and dermal melanin are increased. Emtricitabine is reported to induce hyperpigmentation in the distal extremities in 4% of Asians.[16]

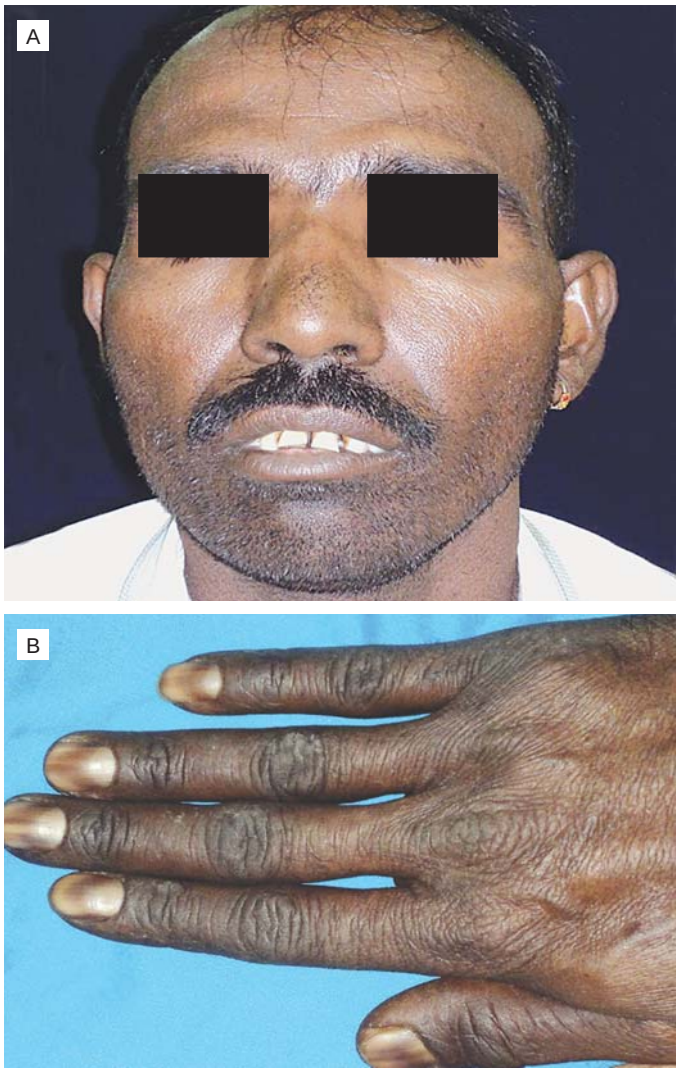

Fig. 23.4: Generalised brownish black pigmentation on face (A) and over hands; (B) in an HIV positive patient on Zidovudine since 15 months.

Antimalarials

The most common drugs used in this category are chloroquine, hydroxychloroquine, amodiaquine, and quinacrine.[17] Hyperpigmentation is very commonly observed after antimalarial therapy. Chloroquine and hydroxychloroquine can cause blue black generalized hyperpigmentation within 4 months of use in about 25% of the patients (Fig. 23.5). Skin on the shins and pretibial regions, nail bed (Fig. 23.6), and hard palate are commonly affected. Reticulated macular gray pigmentation is also reported.[18] Chloroquine and hydroxychloroquine bind to melanin. There is increased epidermal melanin and dermal hemosiderin deposition. Quinacrine on the other hand induces reversible yellow pigmentation on skin, conjunctiva, and oral mucosa, hence appears as icterus (Table 23.4).

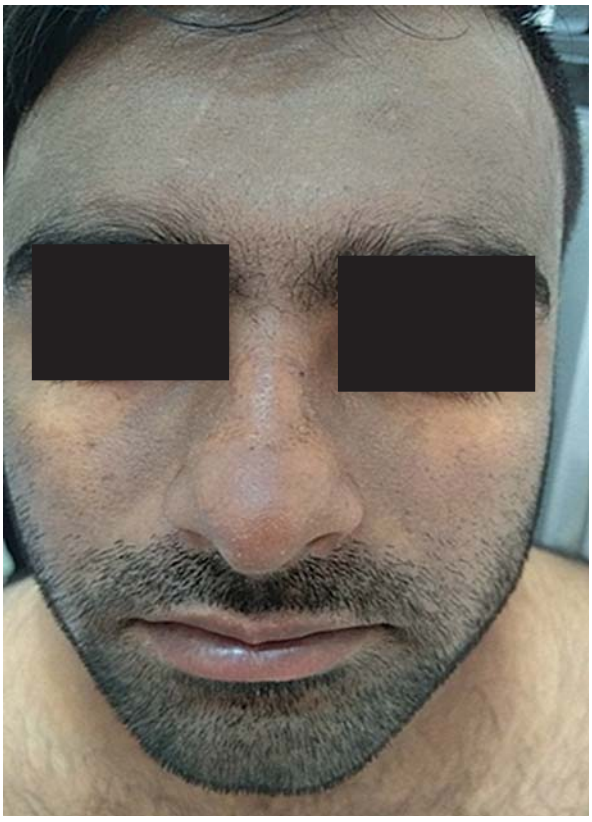

Fig. 23.5: Bluish black pigmentation in photodistribution over face and neck in a young man on hydroxychloroquine since 5 months for erosive oral lichen planus.

Table 23.3: Antiretroviral-induced pigmentation pattern

Drug	Color	Extent	Distribution	Mucosal involvement	Nail
Interferon α + Ribavirin	Brown	Diffuse	Face	+	
Zidovudine	Brown	Diffuse	Areas of friction, palm–soles, photoexposed	+	+ Longitudinal melanonychia
Emtricitabine	Brown	Localized	Distal extremities		

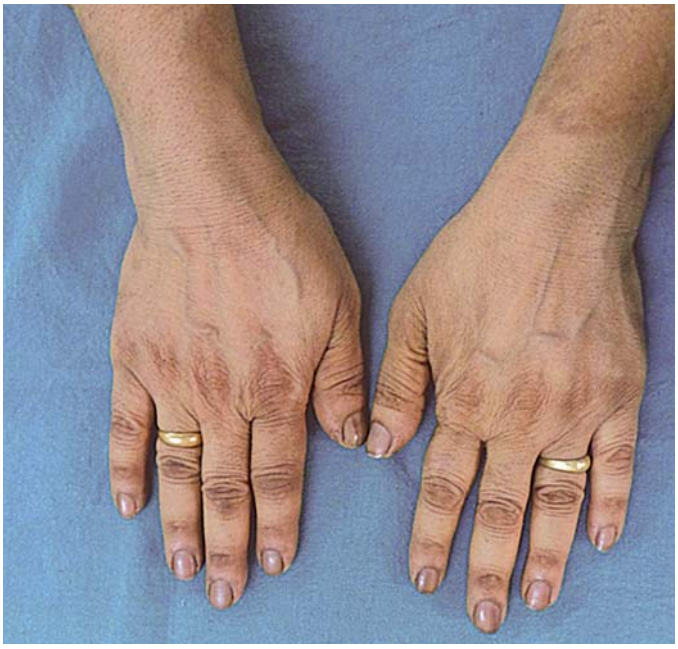

Fig. 23.6: Forty three year old female diagnosed with sarcoidosis on hydroxychloroquine since 7 months showing blue black discoloration of finger nails.

Antipsychotics

Antipsychotic drugs like phenothiazine (chlorpromazine,[19] thioridazine, clozapine[20]) and tricyclic antidepressants imipramine,[21] desipramine and amitriptyline[22] (Fig. 23.7) commonly induce reversible, progressive slate blue pigmentation, which is more intense on exposed areas of the skin. Occasionally, pigmentation in nail beds and corneal and lens opacities are found. Olanzapine can cause abnormal hyperpigmentation of skin and reversible pellagroid skin changes (Fig. 23.8).[23] Newer drugs like ezogabine (retigabine) that is used for treatment of partial seizures in adults has been documented to cause blue-gray mucocutaneous discoloration that affected the face, lips, hard palate, conjunctivae, and nails.[24] Deposited drug may combine with melanin and appear as golden brown

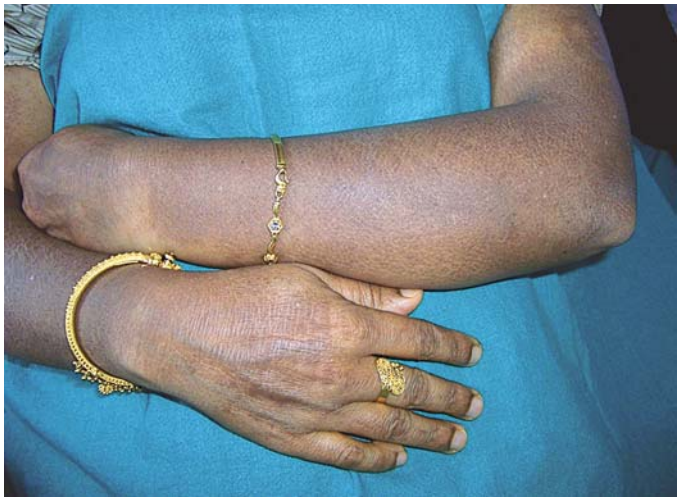

Fig. 23.7: Bluish black pigmentation on sun exposed skin of forearms in a 37 year old female on chlorpromazine since 1 year.

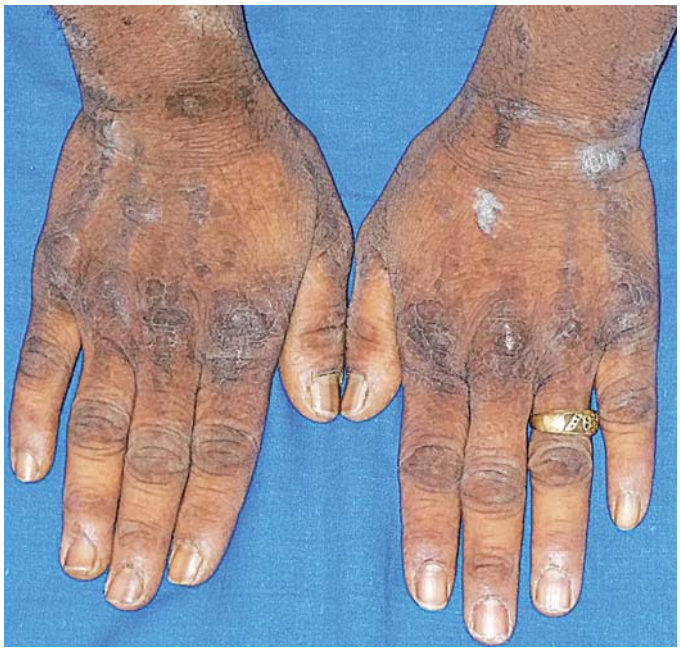

Fig. 23.8: Pellagra like skin changes in a 27 year old patient on olanzapine since 7 months for schizophrenia.

Table 23.4: Pattern of antimalarial-induced hyperpigmentation

Drug	Mechanism and pathology	Color	Extent	Distribution	Pattern	Mucosal involvement	Nail
Chloroquine and Hydroxychloroquine	Increased epidermal melanin and dermal hemosiderin deposition	Blue-black	Generalized	Shins, pretibial regions, face	Reticulated macular pigmentation	+ hard palate and sclerae	+ nail bed
Quinacrine		Yellow	Generalized			+ Oral mucosa and conjunctivae	+

granules in upper dermis around superficial capillaries and electron dense inclusion bodies. Q-switched Nd-YAG laser has been shown to successfully resolve pigmentation caused by imipramine.[25]

Antiacne Antibiotics

Tetracyclines are the group of drugs that cause pigmentary disturbances frequently. Minocycline may cause disconcerting hyperpigmentation in about 3%–5% of patients after long-term use. Apart from long-term cumulative exposure to the drugs, sun exposure and inflammatory conditions are other etiological factors. Three different patterns of minocycline-induced pigmentation are described[26] (Table 23.5). Pigmentation in periorbital area in a serpentine supravenous pattern is reported after use of minocycline.[27–28] Other tissues like nail, sclera, bones, cartilage, thyroid, breast, aorta, and lymph nodes may also be involved. It may take a long time for type I and II to resolve, pigmentation is often gradually reversible after cessation of therapy. Patients treated with Q-switched Nd-YAG/Alexandrite lasers have shown faster resolution.[29–30]

Table 23.5: Patterns of pigmentation with minocycline and histopathological changes

Type	Pattern	Histological feature
I	Type I: Blue-black discoloration in sites of inflammation and acne scars (Fig. 23.9)	Dermal deposition of hemosiderin or iron
II	Blue-gray macules/ patches (1 mm to 10 cm in size) on normal skin usually on arms and legs (particularly shins). This mimics ecchymosis	Dermal deposition of melanin or iron
III	Photodistributed diffuse "muddy brown" pigmentation (Fig. 23.10)	Basal layer melanin
IV	Dyschromia presents within scar tissue specifically on the trunk	Pigment chelated with calcium throughout the dermis as well as within dendritic cells

Heavy Metals

Heavy metals are well known for their ability to induce hyperpigmentation. Most of these get deposited in skin and many of these also stimulate melanocytes to produce melanin. Most of these heavy metals are not used as a drug except few. Human exposure occurs accidentally or unknowingly through some food supplements or through other routes. Arsenic exposure occurs mostly through contaminated drinking water and takes more than a decade of continuous exposure for the pigmentary changes to develop.[31] Although zinc is extensively used in sunblock and is known to be safe, toxicity in the form of pigmentation of mucocutaneous areas, which was confirmed to be due to zinc deposition, is reported.[32] Bismuth is used for treatment of pneumatosis cystoides intestinalis. This gets deposited in the papillary and reticular dermis and leads to pigmentation.[33,34]

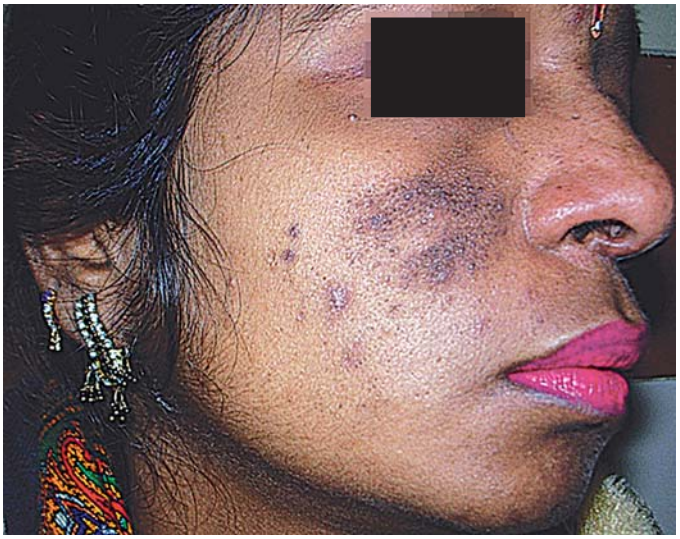

Fig. 23.9: Bluish black pigmentation over healed acne lesions and scars in a patient on minocycline.

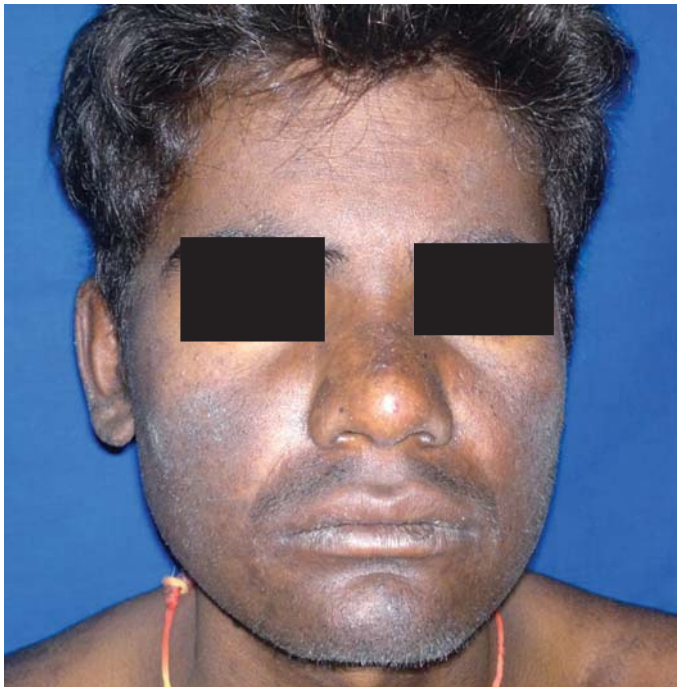

Fig. 23.10: Muddy pigmentation over face in photo distributed pattern in a patient of leprosy on add on Minocycline treatment since 6 months.

Table 23.6: Heavy metals–induced hyperpigmentation

Drug	Color	Extent	Distribution	Pattern	Mucosal involvement	Nail
Arsenic	Bronze	Generalized	Axillae, groin, palms, soles, nipples, trunk and pressure sites (accentuation in folds).	"Raindrops" of lightly pigmented skin (Figs. 23.11 A and B)	± Superimposed	+ Transverse leukonychia (Mee's line)
Bismuth	Blue-gray	Generalized	Face, neck and dorsal hands		+ Oral mucosa and gingivae	
Gold	Blue-gray	Generalized	Sun-exposed areas, mostly periorbital			
Silver	Slate gray	Localized and generalized	Site of application (topical silver sulfadiazine) and exposed areas (systemic)		+ Sclerae, oral mucosa	+ Chromonychia
Mercury	Slate gray	Localized	Skin folds			

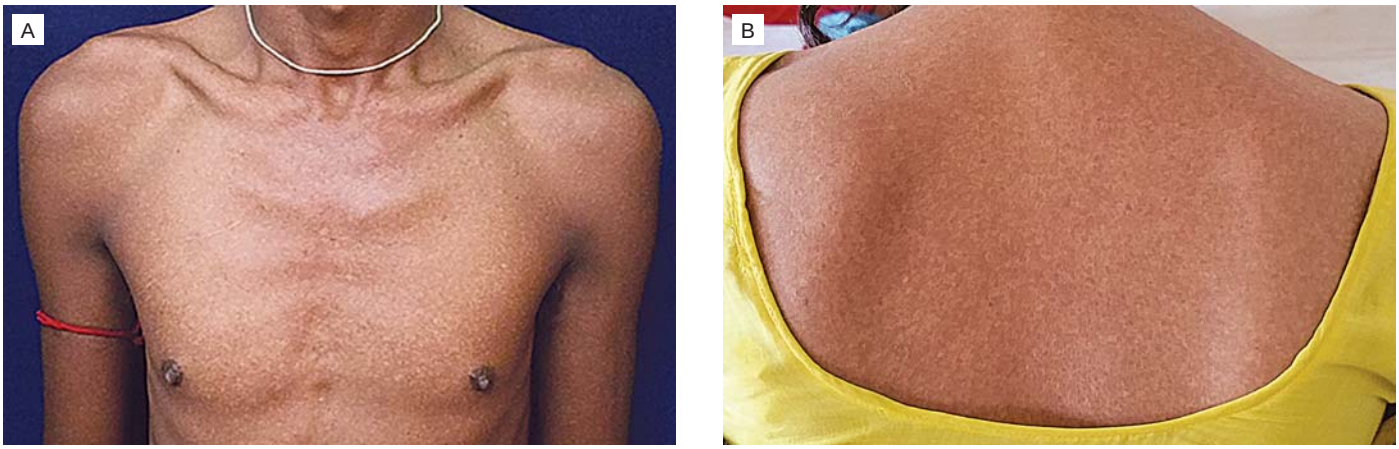

Fig. 23.11: (A & B) Mottled hyper and depigmentation on trunk in arsenicosis.

Exposure to gold can lead to deposition of gold in tissues and skin (chryasis). This is an almost permanent change. This is deposited in perivascular and perieccrine gland areas. Exposure to silver (argyria) can occur through over-the-counter health supplements. Silver is deposited in skin. Sunlight reduces it to elemental silver that gets oxidized to form silver sulfide.[35] Moreover, it stimulates melanin synthesis. The histopathological changes include presence of refractive silver granules throughout the dermis, mainly around eccrine glands and increased melanin within epidermal basal layer and in dermal macrophages. Argyria has been treated with picosecond alexandrite laser.[36]

Mercury may be possibly present in various skin-lightening agents. This metal is reported to toxic to skin and can get deposited leading to hyperpigmentation. In a recently conducted analysis of 549 skin-lightening products, this possible toxicity has appeared to be a real threat globally.[37] On histopathology, metal granule is found to be deposited within macrophages, freely among collagen fibers, or elastic fibers and there is increased epidermal melanin. Table 23.6 summarizes the pigmentary disturbances caused by heavy metals.

Hormones

Hormones such as OCP and adrenocorticotropic hormone (ACTH) are implicated in pigmentary disturbances. OCP cause increased melanin and melanocytosis resulting in melasma (Fig. 23.12) and darkening of nipples and nevi. ACTH can cause melanotic diffuse brown or black pigmentation accentuated in sun-exposed sites.

Miscellaneous Drugs

Amiodarone is reported to cause blue-gray facial pigmentation (Fig. 23.13).[38] Pigmentation may resolve very slowly after discontinuation of therapy or may even be permanent. Yellow-brown granules and lipofuscin is seen in dermal macrophages, mostly in perivascular distribution.

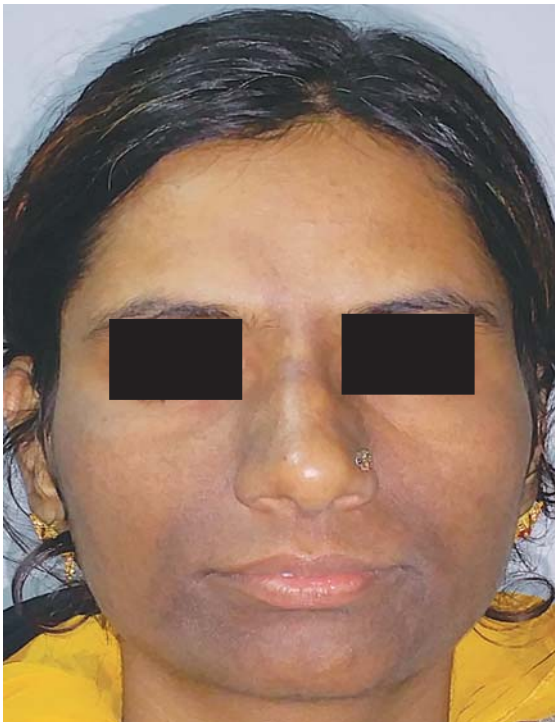

Fig. 23.12: Oral contraceptive pill induced facial pigmentation.

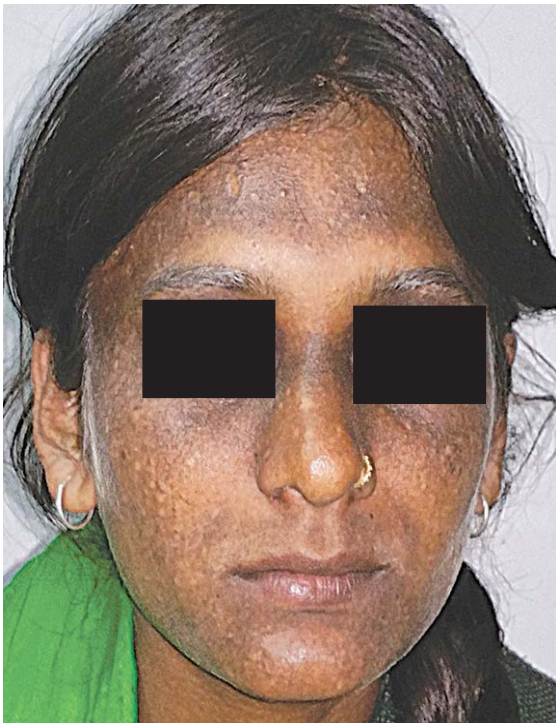

Fig. 23.13: Greyish brown pigmentation over face in a patient on amiodarone since 10 months.

Clofazimine is notorious for inducing pigmentation very rapidly (Fig. 23.14).[39] Drug gets deposited in subcutaneous and visceral fat. After the drug is stopped, it takes many months to spontaneously improve the pigmentation. Hydroquinone applied topically for a prolonged period can occasionally cause ochronosis (Fig. 23.15A).[40] Yellow-brown, banana-shaped fibers are seen in papillary dermis (Fig. 23.15B). Hydroquinone-induced pigmentation may respond to Q-switched lasers and spontaneously improve after stoppage of the drug. Few miscellaneous drugs and their pigmentary patterns are summarized in Table 23.7.

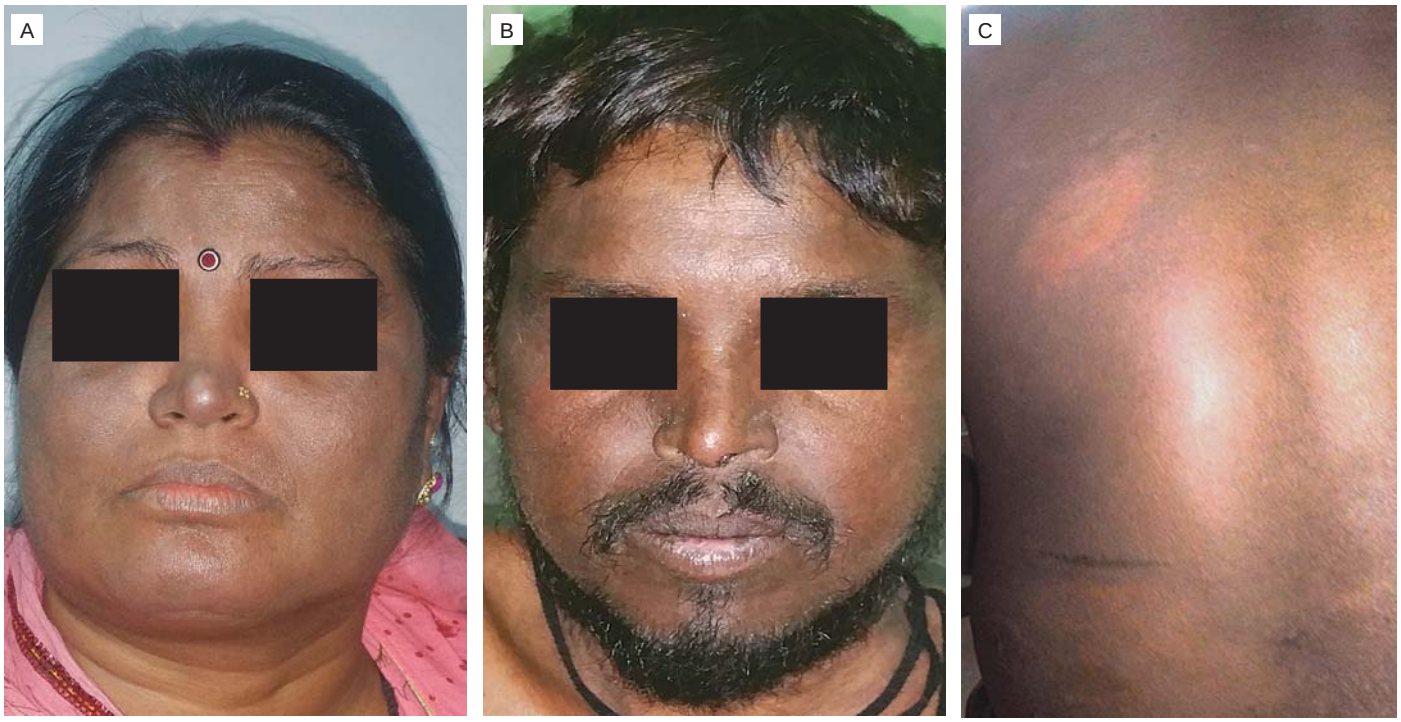

Fig. 23.14: (A–C) Diffuse red brown pigmentation in multibacillary Hansen patients on clofazimine therapy. Note the striking accentuation of Hansen lesions due to increased deposition of dye within the lipid rich lesional skin.

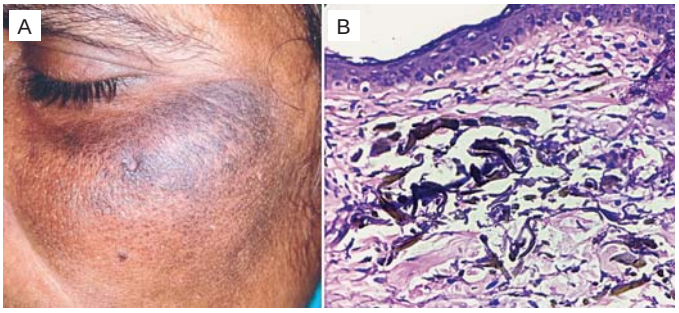

Fig. 23.15: (A) Melasma patient showing caviar like papules and few confetti like depigmented macular lesions after topical 4% hydroquinone therapy for last 7 months; (B) H&E of biopsy cheek showing banana shaped yellowish brown bundles in papillary dermis. (Courtesy of Dr. Keshavamurthy A. Adya, Vijayapur.)

Table 23.7: Miscellaneous drugs causing hyperpigmentation

Drug	Pigment pattern
Amiodarone	Slate blue gray or violaceous pigmentation develops after long-term (>6 months) use of amiodarone predominantly on sun-exposed sites, especially face. Yellowish stippling of cornea may occur.
Clofazimine	Diffuse red to red-brown discoloration of skin, conjunctivae. Pigmentation of gray hair.
Diltiazem[41]	Slate-gray to gray-brown discoloration of sun-exposed skin in patients with skin phototypes IV–VI; perifollicular accentuation and a reticular pattern may be observed.
Hydroquinone	Hyperpigmentation in areas of application due to irritant contact dermatitis (i.e. postinflammatory) or exogenous ochronosis.
Epidermal growth factor receptor inhibitor[42]	Hyperpigmentation and telangiectasia.
Latanoprost[43] Bimatoprost[44]	Eyelid, periocular and perifollicular hyperpigmentation, and darkening of iris.
Psoralens[45]	Diffuse hyperpigmentation after psoralens and ultraviolet A (PUVA). Localized hyperpigmentation after topical psoralens application.
Phenytoin	Reversible melasma-like pigmentation of the face and neck.

Approach to a Case of Drug-Induced Hyperpigmentation

A meticulous history taking recording a temporal association with drug intake and appearance of pigmentation forms an important step in evaluation. However, ascertaining drug causality is not always possible. A long latency, history of multiple drug intake, and difficulty in ruling out other mimickers are some of the factors complicating the scenario. A recently published systematic review of all reports in Medline and Embase, evaluating association of hyperpigmentation and drugs from 1970 until April 2016, concluded that only poor body of evidence exist for an induction of hyperpigmentation by drugs.[46] Causal relationship was found to be likely in only few drugs such as prostaglandins, minocycline, phenothiazine, nicotine, and antimalarial drugs.

Color of pigmentation may be also aid in diagnosis, e.g. heavy metals induce blue-black pigmentation, quinacrine induces yellowish pigmentation, and clofazimine induces red-brown pigmentation.

Distribution and pattern of pigmentation also gives diagnostic clues. Minocycline, apart from causing diffuse pigmentation induces hyperpigmentation on the scars. Pigmentation along veins by bleomycin, involvement of face with dactinomycin, and periocular pigmentation with latanoprost are other typical patterns. Photodistributed pigmentation is found in case of amiodarone, daunorubicin, gold, methotrexate, psoralens, and 5-fluorouracil. The fixed drug eruption (FDE) upon healing leaves behind a characteristic, sharply circumscribed, circular area(s) of pigmentation (Fig. 23.16) that is unmistakable to the trained eye.

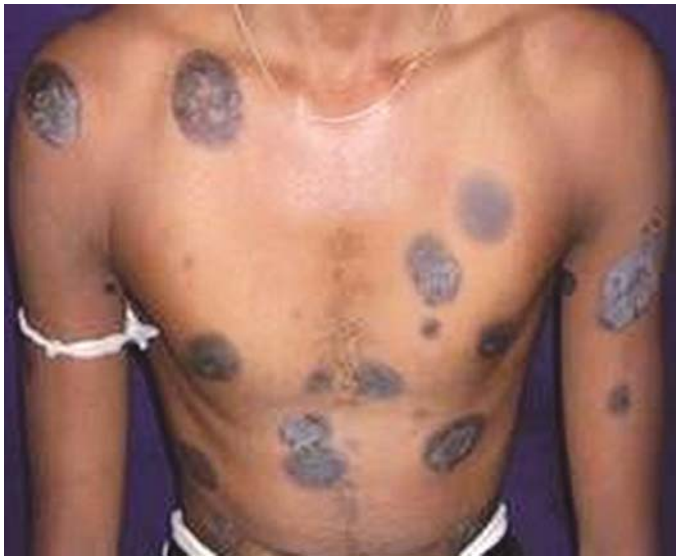

Fig. 23.16: Brown black, strikingly circular pigmentation in healed fixed drug eruption (FDE).

Thorough examination of nails and mucosa is very important in all suspected cases of drug-induced hyperpigmentation. Doxorubicin and imatinib cause oral pigmentation and yellowish stippling of cornea. Nail pigmentation may result from bleomycin, cyclophosphamide, daunorubicin, doxorubicin, and fluorouracil. Methotrexate may induce pigmentation of the hair, while teeth pigmentation may be induced by cyclophosphamide. Reversibility of pigmentation on stoppage is frequent clue to the diagnosis.

Finally, nondrug causes of hyperpigmentation like pigmented contact dermatitis, postinflammatory hyperpigmentation due to other causes, lichen planus pigmentosus, acanthosis nigricans, Addison's disease should be ruled out.

Treatment

Discontinuation of the offending drug is the most important step in management of drug-induced dyschromias. Although when a patient is on multiple drugs, some of which may be lifesaving, the decision requires prudent thinking on part of the consulting dermatologist and the internist. Stopping nonessential drugs may be carried out. A proper counseling about benign and reversible nature of the condition in a significant number of cases may help allaying the patient's distress.

Strict sun protection with physical barriers and sunscreens can help in preventing the worsening of the pigmentation. Bleaching creams and Q-switched Nd-YAG/Alexandrite lasers have shown to be efficacious and may be used in select cases. This has been shown to successfully resolve pigmentation caused by imipramine. Argyria has been treated with picosecond alexandrite laser.

DRUG-INDUCED HYPOPIGMENTATION

Drug-induced hypopigmentation is relatively less commonly observed than hyperpigmentation and can results from direct destruction of melanocytes or inhibition of melanogenesis and melanin transfer. Although, systemic drugs such as Tyrosine Kinase Inhibitors (TKIs) like imatinib, sunitinib, gefitinib, and sorafenib[47] can cause hypopigmentation, the more commoner mechanism is direct cutaneous contact with certain chemicals like phenols and catechols, the so called chemical leukoderma (Fig. 23.17). Arsenic (in a drug or directly through drinking water) can lead to depigmentation as well as hyperpigmentation.

Hypopigmentation following topical drug may be immune-mediated or through nonimmunogenic mechanisms. Topical corticosteroids (TCS) can induce reversible hypopigmentation possibly due to suppression of melanogenesis. Intralesional triamcinolone also commonly induces hypopigmentation in a linear streaky pattern. It is usually associated with variable atrophy in skin (Fig. 23.18).

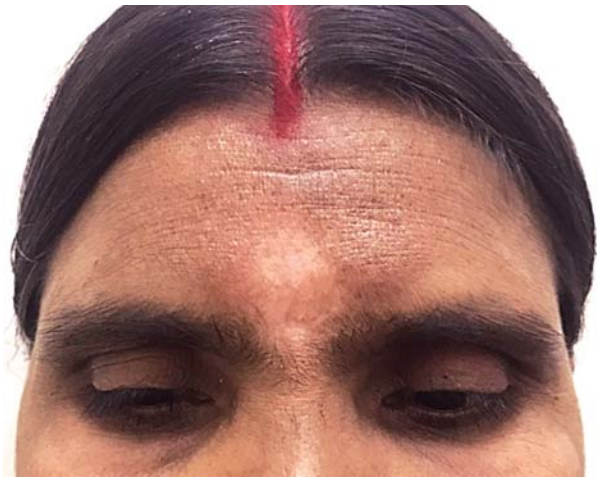

Fig. 23.17: Chemical leukoderma due to para-tertiary butyl phenol (PTBP) in adhesive bindi used by Indian women.

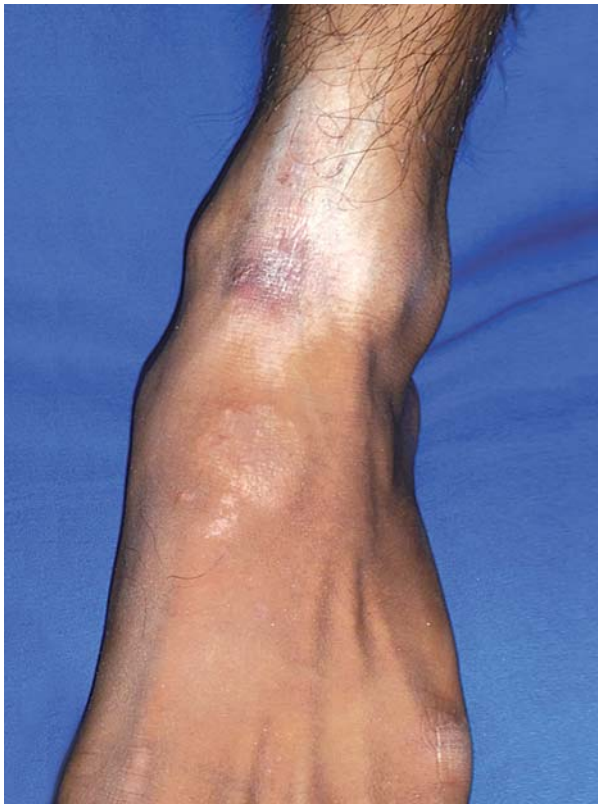

Fig. 23.18: Depigmentation resulting from intralesional triamcinolone injection.

Chemical Leukoderma

Chemical leukoderma (CL) is one important mechanism of hypo- or depigmentation after contact with drugs and chemicals. Both irritant contact dermati-

tis and allergic contact dermatitis may mediate the development of CL.[48] Destruction of melanocytes or sometimes perturbation of some of the melanogenesis pathways leads to depigmentation. Cell destruction occurs through increased intracellular stress, induction of apoptosis, and interleukin (IL6) and IL8 leading to autoimmunity and finally cell necrosis.[49]

Most important chemicals are catechols and phenols that have structural similarity with tyrosine. However, CL encompasses a much wider spectrum of diseases than topical drug-induced leukoderma. Preceding inflammation is not always visible differentiating this from postinflammatory leukoderma.

Some topical and systemic agents that can cause CL are shown in Table 23.8.[50–53]

Drugs Causing Poliosis

Circumscribed loss of pigmentation from otherwise normal hair may be seen with some topical and systemic drugs[50] (Table 23.9).

Management of Drug-Induced Hypopigmentation

Suspected drug has to be withdrawn immediately. However, hypopigmentation may not always be reversible. TCS, calcineurin inhibitor, phototherapy, photochemotherapy, and 308-nm excimer laser have been used. Remarkable improvement after oral pulse steroid therapy has been reported in a case of CL.[58]

Table 23.8: Topical or systemic drugs causing chemical Leukoderma

Amyl nitrate[51]
Arsenic
Azelaic acid
Azo dyes
Botulinum toxin
Chloramphenicol[52]
Chloroquine
Cinnamic aldehyde
Clonidine
Corticosteroids
Eserine
Fluphenazine
Hydroquinone
Imatinib mesylate and other TKIs
Imiquimod[53] (due to benzyl alcohol in vehicle)
Kojic acid
Mercurials
Minoxidil
MBH
Physostigmine
P-phenylenediamine
Squaric acid dibutyl ester
Sulfhydryls
Tansdermal methylphenidate patch (use for the treatment of attention deficit hyperactive disorder)
Thiotepa
Thiotepa (otic preparation)
Tretinoin

MBH - Monobenzyl ether of hydroquinone.

Table 23.9: Drugs causing poliosis

Drugs	Remarks
Topical	
Chloramphenicol[52]	The use after eye surgery can cause eye lash poliosis and hypopigmentation due to allergic contact dermatitis.
Imiquimod[53]	Due to benzyl alcohol present in the vehicle.
PGF2 *a* analogues[54] (Latanoprost and bimatoprost)	Inhibit tyrosinase
Systemic drugs	
Acitretin[55]	It may cause reversible poliosis and alopecia.
Cetuximab[56]	It causes reversible eye lash poliosis and trichomegaly.
Chloroquine	–
Ipilimumab,[57] anticancer drug, (anti-CTLA-4 monoclonal antibody).	
Sunitinib	Causes intermittent leukotrichia

Source: McKee et al.[50]; Rathod and Shuttleworth[52]; Sriprakash and Godbolt[53]; Chen et al.[54]; Chappell et al.[55]; Rodriguez and Ascaso[56]; Victoria Martínez et al.[57]

LEARNING ESSENTIALS

- Clinicians must be aware of the possibility of drug(s) causing pigmentary alteration of skin and appendages.
- Drug induced hyperpigmentation is much more common than the hypopigmentation.
- Newer, targeted cancer chemotherapeutics and arsenicosis can result in both hypo as well as hyperpigmentary abnormalities.
- Drug-induced pigment changes may spontaneously resolve following withdrawal of offending agents.

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Chapter

24

Nail Changes Due to Drugs

Subuhi Kaul • Archana Singal

SUMMARY

Drug eruptions are most commonly encountered adverse drug reactions (ADRs) and can affect anyone. In general, two ADR patterns can be distinguished; acute and chronic. Although acute ADR often constitute medical emergencies and may be life threatening, chronic onset ADR present as dermatological diseases, hair and nail changes. Though several drugs may be responsible for the development of nail abnormalities, only a few classes are consistently associated with nail symptoms. Most commonly implicated drugs are antineoplastic agents, retinoids, antibiotics, antimalarials and antiretroviral drugs. Several pathomechanisms lead to nail changes but the most common is direct toxicity to nail epithelia. Nail abnormalities generally occur as a part of symptom complex with coexistent skin and mucosal lesions. But often, nail changes occur in isolation and may be the initial manifestation of a serious, unsuspected drug-induced adverse reaction. Therefore, it is important for dermatologists to be aware of these changes. Pigmentary abnormalities and asymptomatic growth rate changes are the most commonly observed nail changes and reverse on discontinuation of causative agent. Others are infrequent and include transient nail shedding to permanent nail deformities. A drug should be suspected when multiple or all 20 nails are involved. The changes are often more readily observed on the nails of the thumbs and great toes, and on the fingernails, than on the toenails. The clinical features are dependent on the area of nail unit involved.

INTRODUCTION

Nails act as a window into the human body not only for systemic illness but for drug-related effects too. Effect of drugs on the nail unit can be manifold depending on the part of nail unit affected and the mechanism by which the drug acts. Thus, drugs can affect the color, surface, thickness, and growth rate of the nail, to name a few. Numerous drugs can lead to nail changes, but chemotherapeutic agents are one of the most commonly and consistently implicated group of drugs. A recent Indian study on dermatological adverse effects of chemotherapy reported nail involvement to be the most common, affecting 62% patients.[1] Systemically administered agents account for the majority of the drug-induced nail changes; nevertheless, topical or locally injected agents are not devoid of adverse effects in the nails.

PATHOGENESIS

There are several mechanisms by which drugs cause nail abnormalities (Box 24.1), and not all have been fully elucidated. The clinical features depend not only on the effect of drug but also on the area of the nail unit affected.[2]

Box 24.1: The major mechanisms of drug action on nail[2–4]

- "Cytotoxicity to nail unit epithelia": Considered to be the most common mechanism for antineoplastic drugs. Cessation of mitosis of matricial keratinocytes leads to Beau's lines in the short term and onychomadesis in extreme cases.
- "Elimination and subsequent accumulation in nail plate": This often leads to nail discoloration.
- "Collection of drugs in dermis": Also a cause for nail plate discoloration that may be accompanied by similar discoloration of adjacent skin.
- "Activation of matricial melanocytes": Presents as either longitudinal brown/black bands or diffuse pigmentation of the complete nail.
- "Interruption or alteration of nail blood vessels": Presentation ranges from splinter hemorrhages to Raynaud's phenomenon and skin necrosis.

CLINICAL FEATURES

Drug-induced nail changes reflect the part of nail unit affected. Different clinical presentations, depending on the involvement of the nail unit have been outlined in Table 24.1.

Clinical features can be categorized broadly into the following major headings:

a. Alteration in Nail Color
b. Alteration in Nail Plate Attachment
c. Alteration in Nail Surface
d. Alteration in Shape of Nail
e. Alteration in Growth Rate
f. Nail Changes caused due to Alteration in Blood Vessels
g. Nail changes due to Teratogenesis

Table 24.1 Nail changes according to part of nail unit affected

Component of nail unit	Clinical features
Nail matrix	Beau's lines
	Onychomadesis
	True leukonychia
	Melanonychia (brown to black)
	Nail plate thinning
Nail bed	Onycholysis (hemorrhagic/ nonhemorrhagic)
	Photo-onycholysis
	Apparent leukonychia
	Nail discoloration
Perionychium	Paronychia
	Pyogenic granuloma-like lesions
	Abscesses
Blood vessels	Splinter hemorrhages
	Subungual hematoma
	Raynaud's phenomenon
	Skin necrosis

Alteration in Color (Table 24.2)

Pigmentation Due to Melanin Production

Drug toxicity resulting in induction of matrix melanocytes to produce melanin can give rise to either a solitary longitudinal brown to black band called melanonychia striata (Fig. 24.1) or diffuse nail plate pigmentation (Fig. 24.2). The site of origin is usually the distal matrix.[2]

Fig. 24.1: Melanonychia striata in a patient on chemotherapy.

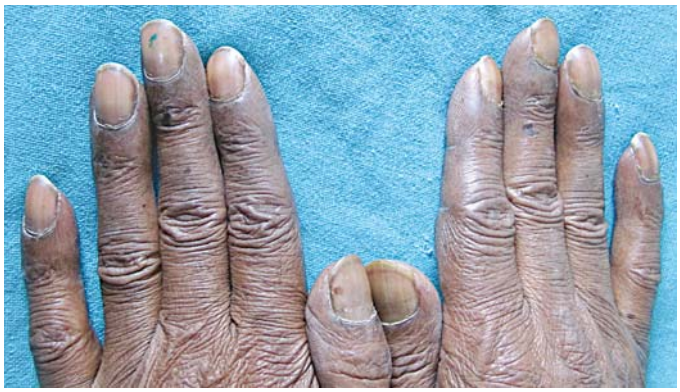

Fig. 24.2: Diffuse nail pigmentation due to antiretroviral therapy (ART).

Melanonychia consequent to activated matrix melanocytes is often seen with chemotherapeutic agents, most frequently with cyclophosphamide, hydroxyurea, and doxorubicin.[3] Numerous others drugs are also implicated, that include methotrexate (Fig. 24.3), daunorubicin, bleomycin, 5-fluorouracil (Figs. 24.4 and 24.5), docetaxel (Fig. 24.6), dacarbazine, melphalan, imatinib, and tegafur.[2–5] This can have an alternate arrangement with intervening normal nail, with every pigmented band corresponding with a chemotherapy cycle.[2,5] The pigmentation first appears 3–8 weeks after the initiation of chemotherapy and is more common in dark skin types as well as in those receiving combination chemotherapy.[5] Transverse melanonychia (Fig. 24.7) is also known to occur especially with electron beam therapy and radiation therapy.[3,5] Other causes include psoralen and ultraviolet A (PUVA), infliximab, zidovudine, phenothiazines, and illicit synthetic alpha-melanocyte-stimulating hormone(α-MSH) analog injections.[5–7]

Drug-induced melanonychia usually affects all or several nails, and is reversible after discontinuation of the offending drug, taking 6–8 weeks for disappearance.[5,8]

Fig. 24.3: Nail Pigmentation in a young girl on methotrexate.

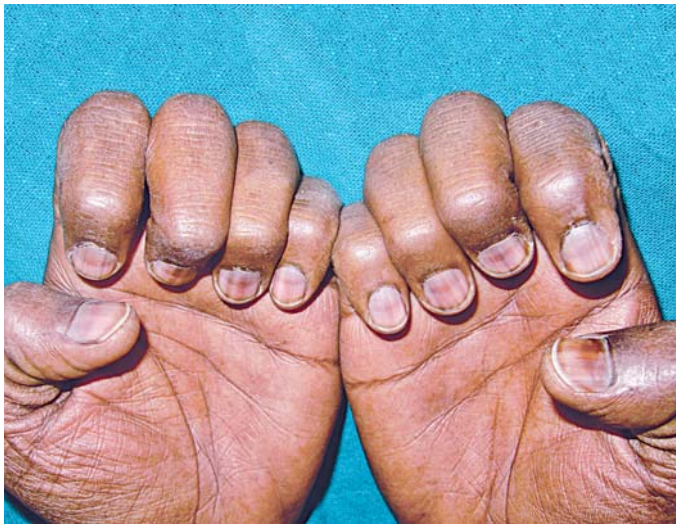

Fig. 24.4: Nail pigmentation due to combination chemotherapy.

Fig. 24.5: Nail pigmentation due to combination chemotherapy.

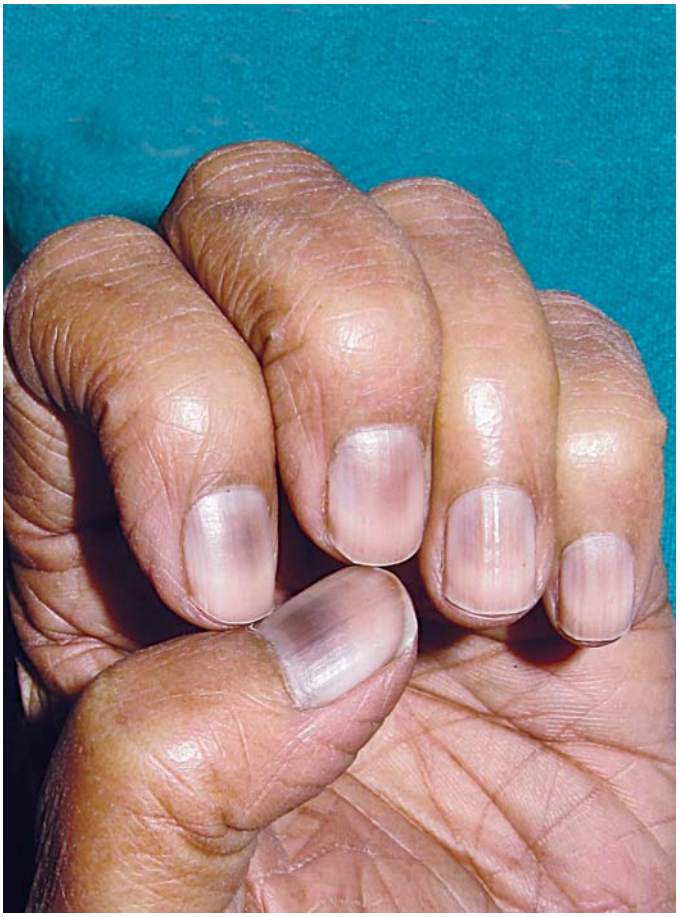

Fig. 24.6: Docetaxel-induced pigmentation in a young woman.

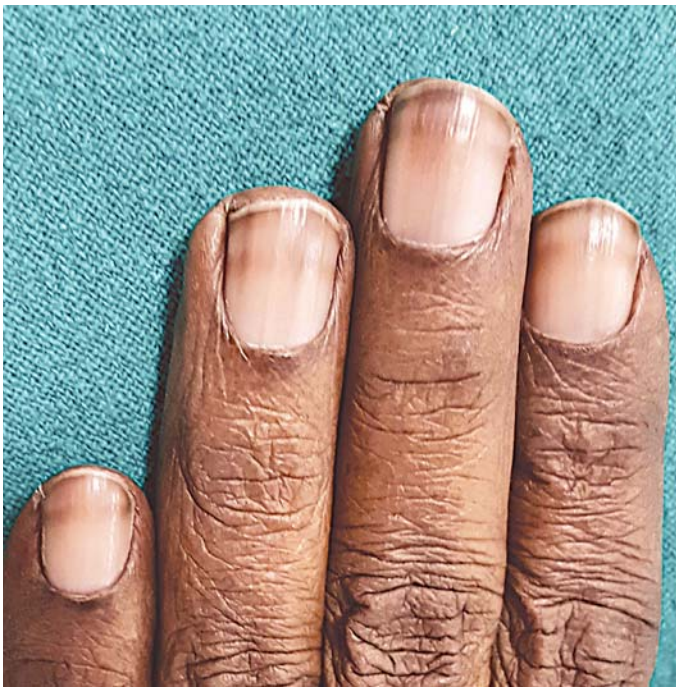

Fig. 24.7: Transverse melanonychia associated with radiation therapy.

Discoloration Due to Other Causes

Drug deposition in the nail plate is the reason for dark brown discoloration observed in patients on clofazimine (Fig. 24.8).[9] Deposition in the nail bed dermis of either a drug or hemosiderin results in a pigmentation that does not move along with nail growth.[2] This is commonly associated with pigmentation of the skin and/or mucosa.

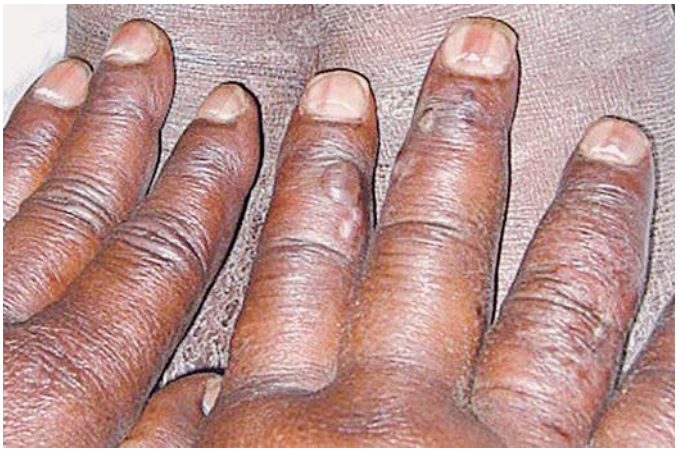

Fig. 24.8: Clofazimine-induced nail pigmentation in patient on multi bacillary multi drug therapy (MBMDT). Note skin pigmentation and acral blistering.

Tetracycline hydrochloride has been known to impart a yellow color to lunula or the entire nail, which fluoresces under Wood's lamp and has been used to check compliance.[5,10] Minocycline-induced nail pigmentation, a blue or slate-gray color (Fig. 24.9) is imparted to proximal part of nails and is attributed to deposition of an iron chelate of minocycline.[5]

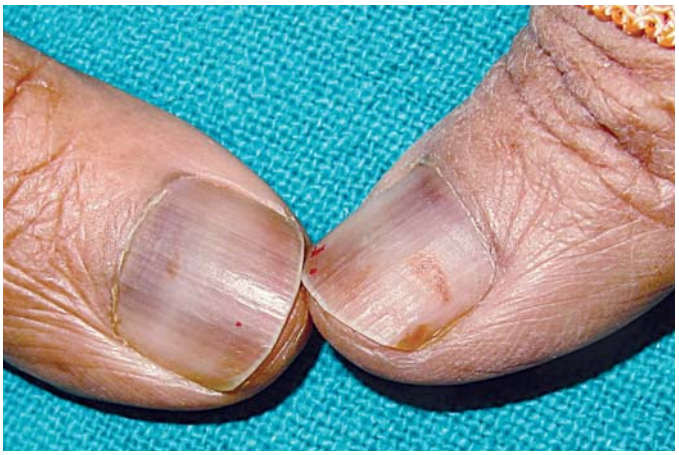

Fig. 24.9: Slate gray pigmentation of minocycline.

Antimalarials such as chloroquine, quinacrine, and mepacrine can lead to blue-brown or blue-black nail color.[5,11] Cessation of drug intake subsequently leads to a diminished intensity of pigmentation that may not disappear completely.

Green discoloration in bilateral nails has been reported with dopamine agonist, rotigotine.[12]

Hemorrhage due to taxanes can leave behind an orange discoloration.[3,13]

Matrix dysfunction ensuing from toxicity of drugs such as cyclophosphamide, vincristine and anthracyclines viz. daunorubicin and doxorubicin leads to true leukonychia.[14–18] A proposed neurogenic mechanism is based on a case report of a lady with complete right sided brachial plexopathy who on treatment with adriamycin and cyclophosphamide developed transverse leukonychia on her left hand nails with sparing of her right hand.[19] Other drugs reported to cause true leukonychia are penicillamine, pilocarpine, cyclosporine, corticosteroids, retinoids, fluorine and sulfonamides.[4]

Apparent leukonychia can be differentiated from true leukonychia by its static nature and disappearance on applying pressure to the nail plate. It results from nail bed abnormalities as the normal pink appearance is a reflection of the underlying bed vasculature. Two clinical presentations are seen in drug-induced cases: Muehrcke's lines and half and half nails.[5,20–22] Muehrcke lines are white transverse bands parallel to the lunula between which is sandwiched between pink band. Although originally described in cases with hypoalbuminemia,[20] Muehrcke lines have also been reported with cytotoxic drugs (Fig. 24.10).[21] The mechanism of formation of Muehrcke lines is still unknown. Half and half nails have a white proximal half, while the distal nail is either pink or red-brown. Half and half nails initially observed in cases with azotemia are also seen as a side effect of chemotherapy drugs.[2,5] Both changes are asymptomatic and disappear with discontinuation of causative drug.

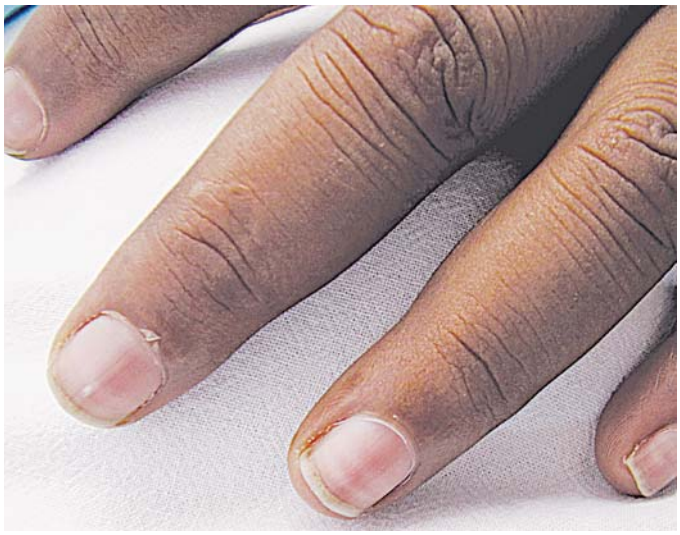

Fig. 24.10: Muehrcke's lines in a patient on chemotherapy for Hepatocellular carcinoma.

Mees' lines characterized by solitary or multiple opaque transverse white bands in the nail plate are typically associated with arsenic poisoning. They are also reported with thallium toxicity, lead, strontium, carbon monoxide poisoning, chemotherapeutics, sulfonamides and pilocarpine.[23–27] A tabulation of the drugs causing nail discoloration is presented in Table 24.2.[5]

Table 24.2: Drugs inducing nail discoloration[5]

Drugs	Color imparted to nail
Acetanilide	Purple
Aniline	Purple
Carbon monoxide	Cherry red
Carotene	Yellow
Chromium	Yellow ochre
Clomipramine	Brown
Erythromycin	Yellow
Heparin	Transverse red lines
Ketoconazole	Longitudinal pigmented bands
Lamivudine	Longitudinal brown/black bands
Lead	Hyperpigmentation/leukonychia
Lithium	Golden
Mepacrine	Yellow/blue-green/grey
Mercury	Yellow to dark brown
Penicillamine	Yellow (as part of yellow nail syndrome)
Phenazopyridine	Lemon yellow
Phenolphthalein	Blue lunulae
Quinidine	Blue-grey transverse lines
Roxithromycin	Brown
Silver	Slate blue
Zidovudine	Black

Alteration in Nail Plate Attachment

Onycholysis is the separation of the overlying nail plate from the nail bed. This can be painful especially in case of taxanes, which can lead to the formation of a subungual hemorrhage and blister (Figs. 24.11A & B). This characteristic hemorrhagic onycholysis may be accompanied by subungual abscesses and is seen more commonly with docetaxel than paclitaxel, reported to occur in up to 44% of patients receiving taxanes.[13] Also reported to result in similar features are doxorubicin, sirolimus, and rituximab.[3,4,28–31] Taxane-induced onycholysis can on occasion be associated with erythema of hands or perimalleolar areas, which was also noted in patients receiving doxorubicin, capecitabine, etoposide, and/or mitoxantrone. The exact pathomechanism of taxane-induced onycholysis remains unknown,[3,32] although

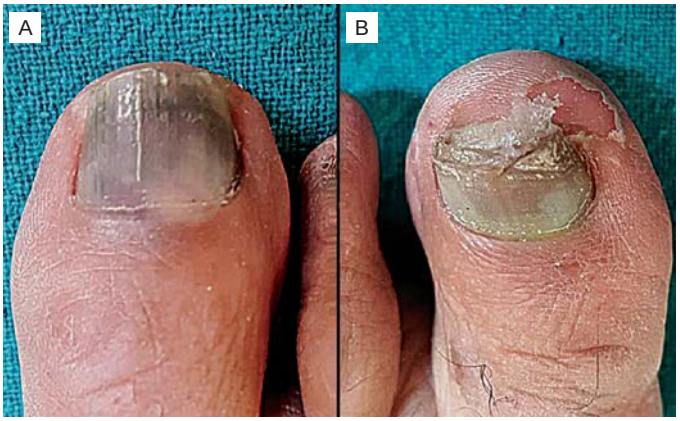

Fig. 24.11: (A & B) Docetaxel-induced subungual hemorrhage and resolving blister on toenails.

it has been proposed to be related to direct nail bed damage, vascular abnormalities, thrombocytopenia or disrupted peripheral nerves.[32] Onycholysis may resolve with dose reduction and usually normalizes spontaneously after drug discontinuation. Retinoids also can sometimes result in onycholysis, probably by increasing nail bed stratum corneum desquamation.[33] Other causative drugs also observed to cause onycholysis are captopril, chloramphenicol, thiazide diuretics and selenium toxicity.[5]

Photo-onycholysis

Photo-onycholysis caused by drugs is due to the separation of the nail plate from the underlying bed, subsequent toxicity by the drug being potentiated by ultraviolet radiation. The onset is two weeks after initiation of drug and can be seen as part of Segal's triad (photosensitivity preceding nail discoloration and onycholysis).[5] Drug-induced photo-onycholysis affects multiple fingers with frequent sparing of the thumbs (Fig. 24.12).[2] Most common drugs

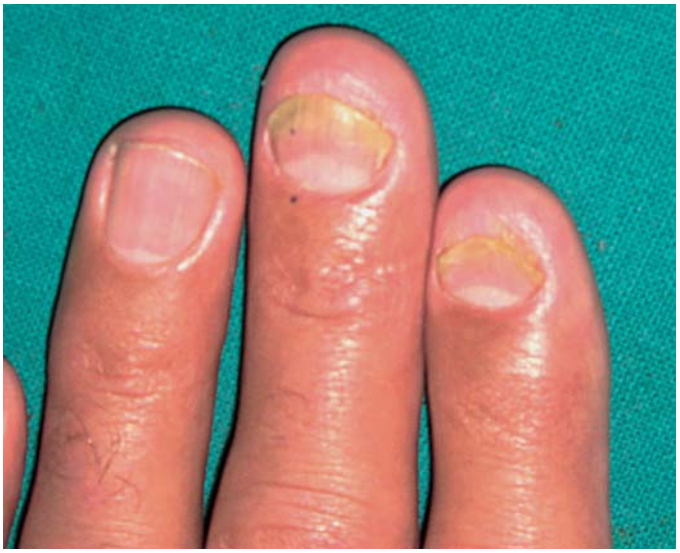

Fig. 24.12: Photo-onycholysis in a patient undergoing PUVA therapy for vitiligo.

implicated are tetracyclines and psoralens (following exposure to either sunlight or artificial light sources). Uncommonly, drugs causing photo-onycholysis are fluoroquinolones, antipsychotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and diuretics. The reported causative agents are tabulated in Table 24.3.[2,5,34]

Table 24.3: Drugs causing photo-onycholysis

Antibiotics
• Tetracyclines
• Fluoroquinolones
• Cephaloridine
• Cloxacillin
• Chloramphenicol
• Sulfonamides
Drugs acting on central nervous system (CNS)
• Benzodiazepines
• Olanzapine
• Aripiprazole
Psoralens
NSAIDs
Griseofulvin
Diuretics
• Indapamide
• Thiazides
Miscellaneous
• Acriflavine
• Chlorpromazine
• Benoxaprofen
• Captopril
• oral contraceptive pills (OCPs)
• Quinine
• Paroxetine
• Sirolimus

Four different types of photo-onycholysis have been observed[5,34]:

Type I: Involvement of multiple fingers. The onycholysis affected part of nail plate is pigmented and half-moon shaped and concave distally with a well-defined proximal border.

Type II: Involvement of a single finger with a well-demarcated circular notch. This opens distally and is of a brownish color proximally.

Type III: Involvement of several fingers wherein the central part of the nail bed has an initial round yellow discoloration which is followed by a reddish color after 5–10 days.

Type IV: Subungual bullae; reported in cases due to tetracycline hydrochloride.

Onychodynia may precede the condition, especially in cases of tetracyclines and psoralens.[34] Photo-onycholysis usually resolves spontaneously after cessation of drug intake. Administration of the offending drug may not always induce a similar episode.[2]

Alteration in Surface

Transverse grooves, longitudinal ridges, trachyonychia are some of the examples of nail surface alteration. Beau's lines are horizontal linear grooves in the nail plate surface that are parallel to the lunula. There may be single or multiple Beau's lines in a nail. They result from a transient diminishing of mitotic activity in the matrix keratinocytes. The timing of systemic insult, duration and severity correspond to the distance from lunula, the width of the groove and the depth, respectively. In its most severe form the nail plate is divided into two parts leading to onychomadesis. Beau's lines are more common on fingernails than toenails (Fig. 24.13). Chemotherapy agents very commonly lead to Beau's lines and onychomadesis. Some examples are 5-fluorouracil, bleomycin and melphalan. Other drugs with which Beau's lines have been reported are dapsone and octreotide. Although onychomadesis has been reported with azithromycin, sulfonamides, parathyroid extract and lead poisoning,[5] onychorrhexis has been noted with thallium toxicity.[35] Increased ridging of nail plate has been observed with phenolphthalein and mercury.[5] Pitting and longitudinal ridging have been reported with fluorine and mepacrine. β-blockers can lead to nail psoriasis and in that context lead to nail plate pits. Elkonyxis, which is a severe full thickness variant of a nail pit, is seen with retinoids and penicillamine.[5,36,37] The known causative agents are tabulated in Table 24.4.[5,35–37]

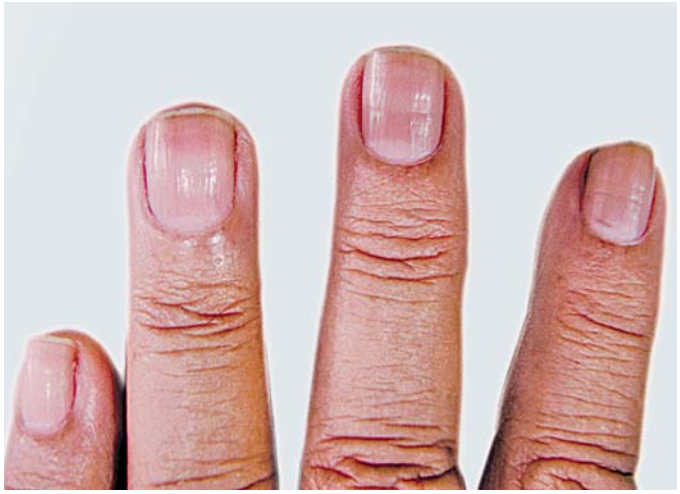

Fig. 24.13: Multiple Beau's lines in a patient on monthly cyclical chemotherapy.

Table 24.4: Drugs affecting nail surface

Nail surface change	Drugs
Beau's lines	Chemotherapeutics, dapsone, octreotide
Onychomadesis	Chemotherapeutics, azithromycin, sulfonamides, parathyroid extract, lead
Onychorrhexis	Thallium toxicity
Increased ridging	Phenolphthalein, mercury
Pitting	Fluorine, mepacrine
Elkonyxis	Retinoids, penicillamine

Alteration in Shape

Flattening of nail was noted in 25% of those with polychlorinated biphenyl toxicity.[38] Ingrown nails have been reported with several drugs including isotretinoin,[5] protease inhibitors (PI) (Fig. 24.14),[39,40] terbinafine,[41] and polychlorinated biphenyl.[5] An unusual adverse effect seen with etretinate has been referred to as "curly nails" wherein the patient developed hemitorsion of the distal nail plates.[42] Pterygium unguis of the toenails is an uncommon side effect of nifedipine therapy.[43] A tabulation of the drugs resulting in changes of shape is given in Table 24.5.[5,38–43]

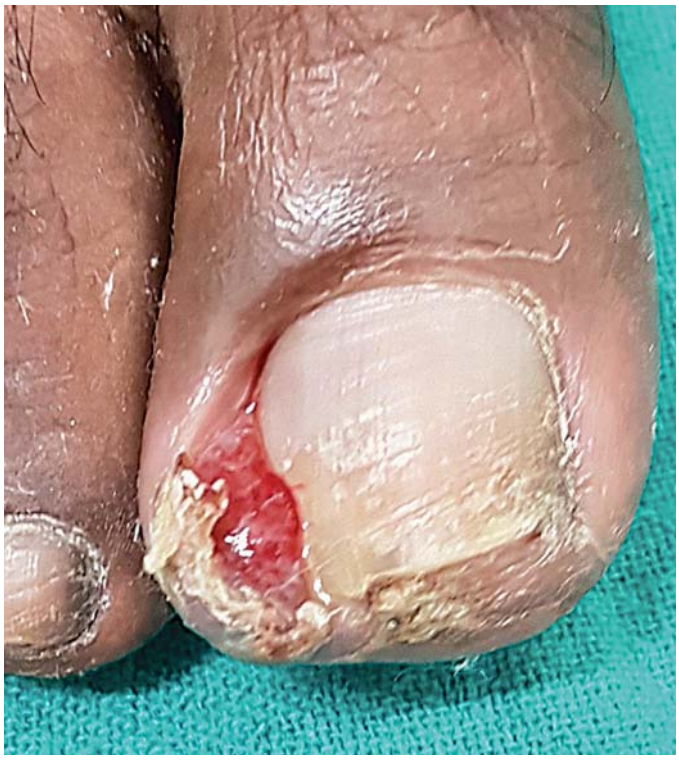

Fig. 24.14: Ingrown toenail in an AIDS patient on Protease Inhibitor.

Table 24.5: Drugs affecting nail shape

Nail shape	Drugs
Platonychia	Polychlorinated biphenyls
Onychocryptosis	Isotretinoin, protease inhibitors, polychlorinated biphenyl
Curly nails	Etretinate
Pterygium	Nifedipine

Alteration in Growth Rate

A number of drugs have been observed to either increase or decrease the rate of nail plate growth. They have been tabulated in Table 24.6.

Table 24.6: Drugs inducing altered nail growth[5]

Increased rate	Decreased rate
Itraconazole	Cyclophosphamide
Fluconazole	Azathioprine
L-dopa	Retinoids
Oral Contraceptive Pills	Heparin
Biotin	Cyclosporine
Cystine	Methotrexate
Methionine	
Gelatin	
Retinoids	

Perionychial Disorders (Table 24.7)

Paronychia refers to erythematous, painful, and edematous condition of the nail folds. Acute paronychia is common with the use of taxanes, systemic retinoids, topical retinoids (viz. tretinoin, tazarotene) protease inhibitors, epidermal growth factor receptor (EGFR) inhibitors, and capecitabine.[2,5,13,44,45] Other drugs include lamivudine, phenolphthalein, and cephalosporins.[5] The pathogenesis is uncertain and

Table 24.7: Drugs causing perionychial disorders

Perionychial disorders	Drugs
Acute paronychia	Taxanes Systemic retinoids Topical retinoids viz. tretinoin, tazarotene Protease inhibitors EGFR inhibitors Capecitabine Less commonly lamivudine Phenolphthalein Cephalosporins
Pyogenic granuloma-like lesions	EGFR inhibitors Retinoids Protease inhibitors

a toxic effect on nail epithelium may be responsible for the resulting inflammation. Methotrexate has been associated with severe exudative paronychia.[2] Pyogenic granuloma-like lesions are often seen arising from the periungual tissue and nail bed with simultaneous involvement of several nails being a characteristic of drug-induced cases. These are frequent with EGFR inhibitors (in up to 60% cases), retinoids and protease inhibitors (6% cases).[2] The pathogenesis is not known but is hypothesized to be due to inhibition of downstream EGFR dependent processes in actively dividing keratinocytes. This leads to decreased keratinocyte proliferation and induction of apoptosis resulting in a thinner periungual epidermis making it easier for the corners of the nail plate to pierce the epidermis and incite an inflammatory reaction. These lesions due to EGFR inhibitors develop after at least 1–2 months of therapy.[3] In case of retinoids, the pathomechanism may be related to decreased attachment between nail keratinocytes, with retention below the proximal nail plate and consequent inflammatory reaction as well as due to their angiogenic properties. Pyogenic granuloma-like lesions usually regress with dose reduction or interruption of treatment. Protease inhibitors may also act by similar mechanisms due to resemblance between active site of HIV-1 protease and retinoic acid-binding protein amino acid sequences. The retinoid receptor may then be activated by the protease inhibitor subsequently leading to an increase in vitamin A activity.[3]

Alteration in Blood Vessels

Hemorrhages

The severity of nail bleeding disorders may range from splinter hemorrhages to subungual hematomas. Toenails are more often affected than fingernails due to repeated injury. Subungual hemorrhages are also seen in association with drug-induced photo-onycholysis, especially in cases due to fluoroquinolones. Chemotherapy-induced thrombocytopenia can cause hematomas and subungual splinter hemorrhages. Taxanes are well known for painful hemorrhagic onycholysis and subungual abscesses (Fig. 24.11). Other drugs causing subungual bleeding are doxorubicin, sirolimus, rituximab, sorafenib, and sunitinib. Two other groups of drugs commonly implicated are NSAIDs such as aspirin and anticoagulants such as warfarin. Retinoids, ganciclovir and ketoconazole are also uncommon causes.[2,5,13]

Ischemic Changes

Ischemic changes vary from Raynaud's phenomenon to digital tip necrosis. Raynaud's phenomenon has been reported with bleomycin (both systemic and intralesional), cyclosporine, β-blockers, clonidine, polychlorinated biphenyl toxicity, and toxic oil syndrome.[2,5] Digital gangrene can be a serious side effect of β-blockers.[46] Stopping the intake of drug may not result in reversion of ischemic signs.

DRUGS INDUCING NAIL CHANGES

Though several drugs, both systemic and topical can induce changes in the nails, some group of drugs more commonly associated with nail changes. Tables 24.8–24.10 summarize the commonly used classes of drugs and the nail changes induced by them.

Table 24.8: Antimicrobials causing nail changes

	Nail changes
A. Antibiotics	
Tetracyclines	Photo-onycholysis, Yellow lunulae/entire nail
Cephalosporins	Photo-onycholysis, onycholysis, onychomadesis, acute paronychia
Chloramphenicol	Photo-onycholysis, onycholysis
Clofazimine	Brown discoloration
Quinolones	Photo-onycholysis
Roxithromycin	Brownish discoloration
Erythromycin	Yellowish fingernail discoloration
Azithromycin	Onychomadesis
Sulfonamides	Onychomadesis, Beau's lines, leukonychia, decreased nail growth rate, paronychia
Dapsone	Beau's lines
B. Antifungals	
Itraconazole	Increased nail growth rate
Fluconazole	Increased nail growth rate
Ketoconazole	Splinter hemorrhages, longitudinal pigmented streaks
Terbinafine	Onychocryptosis
Amorolfine	Blue/yellow-brown discoloration, Amorolfine nails
C. Antiretroviral drugs	
Nucleotide analog reverse transcriptase inhibitors	Melanonychia, paronychia, pyoderma gangrenosum like lesions, decreased nail growth
Protease inhibitors	Pyogenic granuloma-like lesions, paronychia, onychocryptosis, onycholysis

Table 24.9: Chemotherapeutic agents and nail changes

Drug	Nail changes	Drug	Nail changes
Cyclophosphamide	Melanonychia, decreased nail growth, erythema of proximal nail fold and onychodermal band	**Melphalan**	Melanonychia, Beau's lines
Doxorubicin	Melanonychia or diffuse blue/brown/grey/black pigmentation of nail plate, onycholysis	**Busulfan**	Brown longitudinal bands
Bleomycin	Melanonychia, dark cuticles, brittle nails, Beau's lines, onycholysis, onychomadesis, Raynaud's phenomenon, gangrene, sclerodermatous changes, acropachy	**Cisplatin**	Black longitudinal bands, digit tip necrosis
Methotrexate	Melanonychia, reduced nail growth, paronychia, onychomadesis	**EGFR inhibitors**	Pyogenic granuloma-like lesions, paronychia
5-Fluorouracil	Melanonychia, brittle nails, Beau's lines, paronychia, onycholysis, onychomadesis, half and half nails	**Hydroxyurea**	Melanonychia, brittle nails, onychoschizia, onycholysis
Paclitaxel and Docetaxel	Hemorrhagic onycholysis	**Dacarbazine**	Brown discoloration

Table 24.10: Miscellaneous drugs leading to nail disorders

Drug	Nail changes
Anticonvulsants	Teratogenicity (nail hypoplasia)
Psoralens	Photo-onycholysis
Retinoids	Nail thinning, softening, splitting, and fragility Nail growth rate may be decreased (more common), normal or increased Onycholysis, elkonyxis, curly nails Paronychia, pyogenic granuloma-like lesions
Heavy metals:	
Arsenic	Mee's lines, Beau's lines, onychomadesis, melanonychia, diffuse black or brown discoloration of nail plate
Silver	Blue-black pigmentation of periungum, slate-blue discoloration of lunulae
Mercury	Nail plate ridging, fragility, discoloration, nail loss
Gold	Yellow-brown discoloration, nail plate thinning, brittle nails, onycholysis, Onychomadesis, nail loss
Lead	Leukonychia, onychomadesis
Thallium	Brown discoloration, onychorrhexis, transverse leukonychia

Topical Drug—Induced Nail Changes

Topical medicaments also lead to nail unit abnormalities albeit infrequently, either due to toxicity or irritating properties.

- "Amorolfine" has been reported to result in yellow-brown nail plate discoloration, a specific side effect called "amorolfine nails," observed in patients who file their nails excessively leading to a thin distal nail plate and reddened nail bed.[47]
- "Topical hydroquinone" can lead to an orange-brown hue of the nails.[48]
- Brownish discoloration has been observed in those using water with high "iron" content.[5]
- "Phenols and catechols, p-phenylenediamine, mercurials, arsenic, corticosteroids, tretinoin, and azelaic acid" can result in chemical leukoderma.
- Use of prolonged "corticosteroids" may cause digital tip atrophy and result in "disappearing digit".[49]

Several topical agents can elicit an irritant or allergic reaction of the periungual tissues resulting in eczematous changes e.g. urea preparations, imidazole derivatives, amorolfine, and nail lacquers containing tosylamide/formaldehyde resin.[2]

Local Injectable Drug Adverse Effects

Bleomycin used intralesionally for warts especially in the periungual regions may in rare cases give rise to sclerodermoid changes of the fingertips, digital necrosis (Fig. 24.16), nail plate ridging, and Raynaud's phenomenon.[0,51]

Intramatricial steroid often used in nail lichen planus and nail psoriasis may cause injection site pain, subungual hemorrhage, leukonychia & nail fold atrophy. Rare reports of rupture of terminal extensor tendon and dermal atrophy are also present.[52]

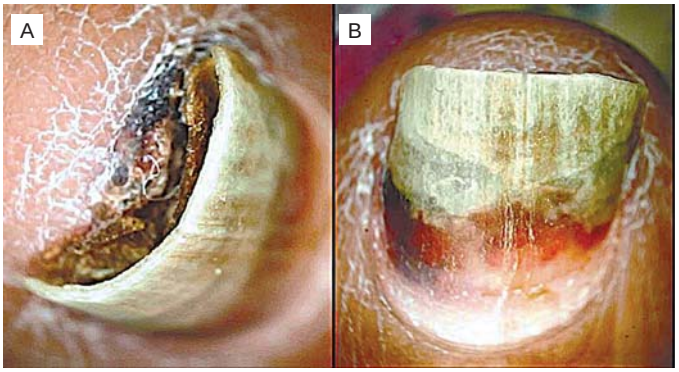

Fig. 24.15: (A & B) Taxane induced subungual hemorrhage leading to onycholysis. (Courtesy of Dr. Sidharth Sonthalia, Gurgaon.)

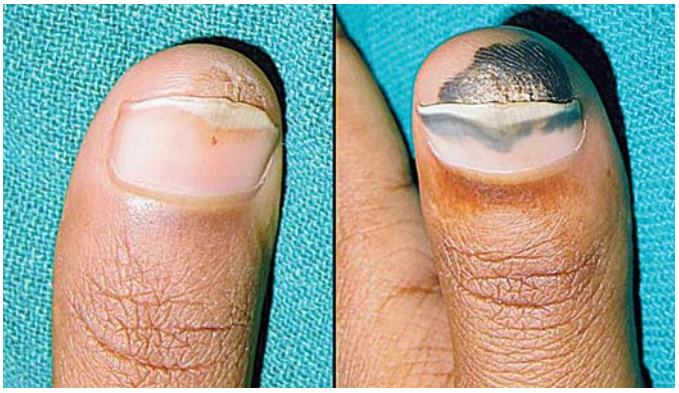

Fig. 24.16: Digital necrosis following bleomycin injection for periungual warts.

Teratogenesis

The main causative agents for fetal nail dystrophy are hydantoin, carbamazepine, warfarin, alcohol, mycophenolate mofetil, and trimethadione, which can lead to hypoplastic nails if there is in utero exposure. Sodium valproate results in hyperconvex nails.[4,5] Mothers exposed to polychlorinated biphenyl contaminated cooking oil during pregnancy gave birth to children with koilonychias, transverse grooves, irregular depressions, hyperpigmented, and flattened nails which could point towards a toxic effect on the fetal nail matrix.[53]

DIAGNOSIS

Drug-induced nail changes usually involve several or all nails. A detailed clinical history is essential to establish a temporal correlation and diagnosis. However, following factors often pose a challenge:

1. The nail changes most often appear weeks after drug initiation.
2. All nails are not necessarily involved.
3. Nail changes can improve without drug cessation.
4. Unlike cutaneous ADR, rechallenge is usually negative in nails.

Drug-induced pigmentation uncommonly affects solitary nail and in such cases it is imperative to rule out melanoma by dermoscopy or nail histopathology when in doubt.

TREATMENT

Most of the drug-induced nail changes are reversible and do not require specific treatment. However, certain conditions such as paronychia, pyogenic granulomas, and ingrown nail demand attention and should be appropriately managed.

- Camouflaging nail plate discoloration with nail varnish is a simple remedy for those perturbed by the appearance of their nails.
- Oral biotin may be used for the treatment of brittle nails.
- Topical application of hydroxypropyl chitosan may lead to increased growth rate of nail.[3]
- In case of paronychia, topical and oral antimicrobials might be required along with topical steroid in case of chronic cases.
- A reduction in retinoid dose has been reported to allow resolution of nail symptoms.
- A change in antiretroviral drug regimen may be considered if pyogenic granuloma-like lesions are distressing or disabling.
- Topical steroids and antibiotics can help reduce exudation and inflammation. Paronychia frequently resolves with cessation of drug intake and is usually followed by onychomadesis.[2] For ingrown toe nails cushioning inserts inside shoes and pain control may allow a conservative approach.[45] The need for systemic or topical antibiotics should be assessed in case of secondary infection.
- A recent study reported the benefit of application of autologous platelet-rich plasma for paronychia.[54]

PREVENTION

Some general measures can help prevent certain drug-induced nail changes.

- All patients on drugs such as tetracyclines should be instructed to avoid prolonged sun exposure and informed of the benefit of applying an opaque colored nail varnish, which protects the nail bed from light.
- In case of those on antineoplastic agents, especially EGFR inhibitors, preventive measures

for paronychia should be taken. Avoidance of overzealous manicures and toluene/formaldehyde containing nail lacquers and nail polish removers should be advised. Regular use of an emollient and protective gloves during work involving contact with water or detergents can help decrease further nail fold damage.

- To decrease repeated trauma to toenails and prevent ingrown nails regular trimming of nails ensuring the distal edge is straight along with wearing wide-fitting footwear is recommended.[3]
- Studies done using frozen gloves and socks in patients receiving taxanes have successfully brought down the incidence rates of taxane-induced onycholysis and cutaneous toxicity.[55,56]

LEARNING ESSENTIALS

- Drug-induced nail changes should be suspected in any patient with abnormalities of several or all nails.
- Most commonly implicated drugs are antineoplastic agents, retinoids, antibiotics, antimalarials and antiretroviral drugs.
- The most common pathomechanism is thought to be direct toxicity to nail epithelia.
- Nail abnormalities can occur along with cutaneous/mucosal changes (more common) or in isolation.
- Nail discoloration and growth rate alteration are the most commonly observed nail changes.
- The nail changes usually resolve (within 6–8 weeks) on discontinuation of the offending agent.

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Chapter

25

Drug Reactions Affecting Mucosae

Rajesh Datt Mehta • Vaishali Masatkar • Divya Sharma

SUMMARY

The mucosal adverse drug reactions (MADRs) may occur as a sole manifestation or be a component of accompanying cutaneous manifestation of drug reaction. Most MADRs are benign and non-consequential but they may sometimes be a component of severe cutaneous adverse reactions (SCARs) and have detrimental consequences. Oral mucosa is most commonly involved in MADR followed by ocular. Alternative medicinal therapies may also be causal, accounting for the underestimated, under-diagnosed, and under-reported MADRs. Newer biological agents also have been reported to cause MADRs. Assessment of causative culprit drug depends on the art of exhaustive history taking and keeping a high index of suspicion. Basic principles of management of MADR include immediate withdrawal of the offending drug, maintenance of local hygiene, symptomatic management, and specific therapy.

INTRODUCTION AND CLASSIFICATION

Mucosal anatomy, physiology, and biochemical milieu make this site susceptible, alarming, and discomforting target for several diseases including drug reactions. The mucosal affection by drugs may occur in isolation or be a part of more extensive mucocutaneous drug reaction. The lesions may resemble many idiopathic diseases affecting mucosae and the diagnosis may be missed unless a high degree of suspicion is kept. A relatively limited number of reaction patterns are seen in the mucosae compared to skin, possibly due to higher turnover rates, particularly in the oral mucosa.[1]

There is no uniform method to classify mucosal adverse drug reactions (MADRs). They can be classified depending on primary involvement, severity, and anatomical site involved.

Primary Involvement

1. ***Isolated MADR*:** These have only mucosal component without accompanying cutaneous and systemic involvement (oral ulceration, aphthae,mucositis, fixed drug eruption, etc.).
2. ***Associated MADR*:** This group consists of mucocutaneous adverse drug reactions (ADRs) with or without systemic manifestations [e.g., Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), generalized bullous fixed drug eruption (GBFDE)].

Severity

1. ***Benign MADRs***

   Benign MADRs do not mean asymptomatic lesions but suggest that the condition has a self-limiting course. Most of the times, these are non-progressive and non-consequential. Examples include fixed drug eruption (FDE), pigmentation, aphthous ulcers, and cheilitis.

2. ***Severe MADRs***

   Severe MADRs are associated with unbearable burning, pain, stinging, large ulcers, and extensive cutaneous as well as systemic symptoms. Examples include SJS, erythema multiforme (EM), TEN, GBFDE.

Anatomical

Based on the predominant site affected, MADR may be classified as: oral, ocular, genital, nasal or anal. Many times several mucosae are simultaneously affected, particularly in severe cutaneous adverse reactions (SCARs).This chapter describes MADRs according to the anatomical classification.

ORAL CAVITY

Oral mucosa is the most common and easily discernible site affected in MADRs. The various clinical presentations of MADRs in oral cavity may be grouped as in Box 25.1.

Box 25.1: Various MADRs involving oral mucosa

- Aphthous ulcers and stomatitis
- Xerostomia
- Dysesthesia
- Fibrovascular hyperplasia
- Infections
- Keratoses
- Lichenoid reaction
- Mucositis
- Neuroangioedema
- Pigmentation
- Vesiculobullous eruptions
- Osteonecrosis of jaw
- Malignancy
- Hemorrhage

Stomatitis and Aphthous Ulcers

Stomatitis

The sore feeling with smarting sensation, commonly perceived as rawness in oral cavity can result from caustic agents, mouthwashes, swish rinses, and systemic antihistamines.

Aphthous Ulcers

Drugs are one of the many causes of aphthae which are characterized by well-defined round to oval ulcers of up to 5–10 mm size with a dirty yellow fibrinous slough surrounded by an erythematous halo. Important component of drug-induced stomatitis and aphthae is that these are reversible upon withdrawal of therapy, unlike idiopathic recurrent aphthous ulcers. Drugs causing aphthous ulcers and stomatitis are mentioned in Table 25.1.

Table 25.1: Drugs causing aphthous ulcers and stomatitis[2-7]

Drug category	Drugs
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Piroxicam (Fig. 25.1) Phenylbutazone Naproxen Cyclooxygenase-2 inhibitors (Rofecoxib)
Anti-hypertensive drugs	Calcium channel blockers (nicorandil) β-blockers ACE inhibitor and ARB (captopril, losartan)
Immunosupressants and immunomodulatory drugs	Azathioprine Mycophenolate mofetil Sirolimus Methotrexate Cancer chemotherapeutic agents (5-FU, cisplatin, hydroxyurea)
Others	Gold salts Alendronate

ACE - angiotensin converting enzyme, ARB - angiotensin receptor blocker

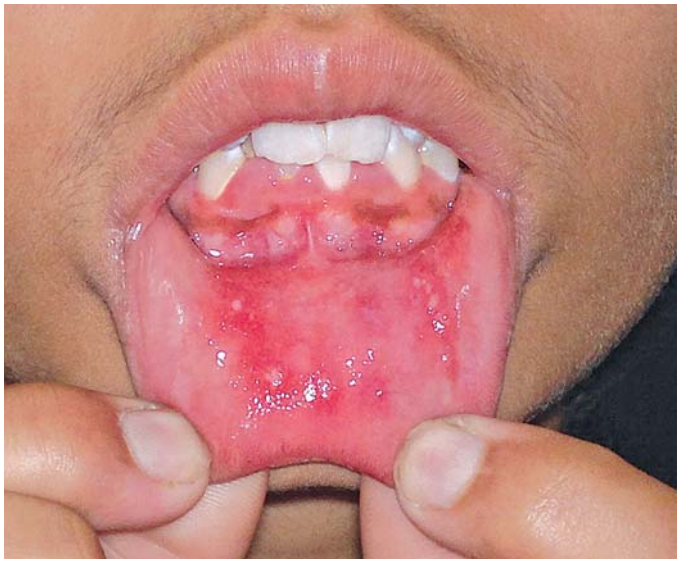


Fig. 25.1: Aphthous ulcers like lesions in oral cavity, suspected to be due to piroxicam intake.

Xerostomia

Medications are one of the most common causes of both xerostomia and hyposalivation.[1] The elderly are more prone to develop this because of increasing number of medications used by them. There is a feeling of dryness in the oral cavity. Decreased salivation may lead to frictional trauma, erythema, and orodynia. Increased incidence of candidiasis and bacterial stomatitis may be seen. In a systematic review, xerostomia was reported to be one of the most common oral adverse effects, associated with over 80% of the 100 most prescribed medications.[8] The most frequently reported drugs causing xerostomia are antidepressants, antipsychotics, antihistamines, muscarinic receptor, α-receptor antagonists, antihypertensives [e.g., diuretics, β-blockers, and angiotensin-converting enzyme (ACE) inhibitors], bronchodilators, and skeletal muscle relaxants.[9,10]

Dysesthesia and Dysgeusia

Dysesthesia refers to sensations in the oral cavity without clinical signs on examination and include altered sensation, burning and dysgeusia. It has also been labeled as burning mouth syndrome. Hyposalivation is a common accompaniment and it has been considered that dysesthesia is always secondary to drug-induced hyposalivation. Conventional chemo-

therapeutic agents (taxanes, platinum compounds, vinca alkaloids), newer targeted agents such as vismodegib, sunitinib, sorafenib are the most common class of drugs causing dysesthesia[1,11–13]. Other drugs include macrolides, terbinafine, fluoroquinolones, proton pump inhibitors, ACE inhibitors and statins.

Various mechanisms postulated in dysesthesia are the following:[11]

1. Drug-receptor inhibition
2. Altered neurotransmitter function
3. Disturbed neuronic action potential
4. Disturbed central sensory modulation

Drugs causing taste disturbance include antibiotics, ACE inhibitors, aspirin, diclofenac, diltiazem, metronidazole, propranolol, and sulfonamides.[14]

Fibrovascular Hyperplasia

Certain drugs[15,16] (Table. 25.2) cause diffuse and nodular overgrowth of the gingival tissue by inducing hyperplasia. This is likely to occur in genetically predisposed patients due to decreased cellular folic acid uptake resulting in decreased activity of matrix metalloproteinases which ultimately leads to failure of collagenase activity. Phenytoin and cyclosporine in addition, cause an increased expression of interleukin 1 and 6 leading to induction of oral mucosal mesenchymal stem cells to differentiate towards a pro-fibrotic phenotype.[1]

Table 25.2: Fibrovascular hyperplasia and drugs

Drug category	Drugs
Calcium channel blockers	Nifedipine Amlodipine
Calcineurin inhibitors	Cyclosporine (Fig. 25.2) Tacrolimus
Anticonvulsants	Phenytoin

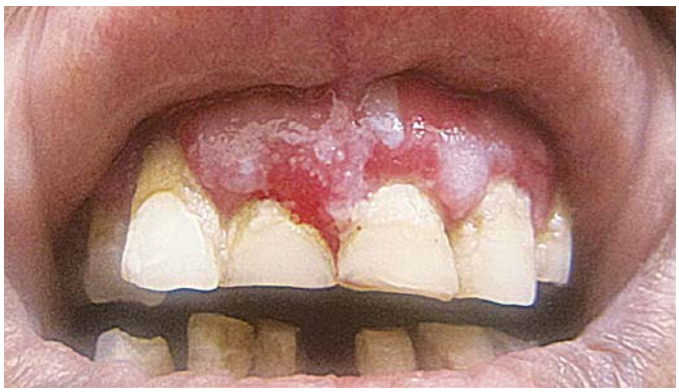


Fig. 25.2: Gingival hyperplasia in a patient on cyclosporine therapy. (Courtesy of Dr. Bela Shah, Ahmedabad.)

Infections

Patients taking immunosuppressants and broad spectrum antibiotics are prone to develop oral candidiasis (Fig. 25.3) due to alterations in commensal oral microflora. Drugs that induce xerostomia may also increase the likelihood of candidal infection by reducing antimicrobial salivary constituents (immunoglobulins, lactoferrin, histatins, lysozyme).[17] Various other opportunistic infections like histoplasmosis, coccidioidomycosis, herpes gingivostomatitis, herpes zoster, tuberculosis etc. may also be seen in patients taking immunosuppressants.[18] Newer biological agents may also predispose to various infections.[19]

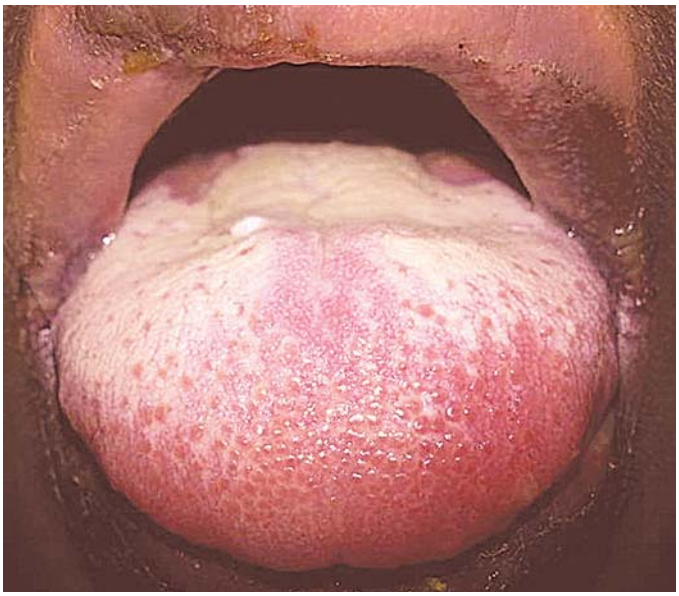


Fig. 25.3: Hyperplastic candidiasis in a patient on methotrexate.

Keratosis

Thickness of oral mucosae with whitish plaque formation has been reported with palifermin, a recombinant keratinocyte growth factor used to reduce the incidence and severity of mucositis following chemotherapy, radiotherapy, and hematopoietic stem cell transplantation.[20]

Lichenoid Reaction

Drug-induced oral lichenoid reactions or oral lichenoid lesions were first cited in 1971 by Almeyda and Levantine.[21] Many cases were documented among United States military personnel during the war in the Pacific, Southeastern Europe, and Indonesia, attributed to prophylactic use of antimalarials. Since then, many drugs[22–26] have been associated; the most common agents being NSAIDs, and ACE. The presence of "thiol" group in the drugs such as piroxicam,

sulfasalazine, and glipizide has been shown to play a role in inducing lichenoid drug reaction. Oral lichenoid reaction can affect buccal mucosae, gingiva or tongue and may show classical reticulate pattern or erosive type of lesions as seen in idiopathic lichen planus.[1] The appearance of oral lichenoid reactions following medication has variable latency period lasting from several weeks to several years and depends on many factors such as the type, dosage, and previous exposure to the drug. The cutaneous lesions if present aid in the diagnosis. Table 25.3 lists the common drugs causing lichenoid drug reactions.[21–26]

Table 25.3: Drugs causing lichenoid drug reactions

Drug class	Drugs
Anticonvulsants	Carbamazepine, phenytoin
Antihypertensives	Captopril, propranolol, procainamide, methyldopa, labetalol
Analgesics	Piroxicam, phenylbutazone
Antidiabetics	Chlorpropamide, metformin, tolbutamide
Antimalarials	Chloroquine, hydroxychloroquine, quinine
Antifungals	Griseofulvin, ketoconazole
Antimicrobials	Metronidazole, niridazole, penicillins, sulfonamides, tetracyclines, streptomycin, rifampicin, prothionamide, levamisole, lincomycin
Antipsychotics	Barbiturates, chloral hydrate, lorazepam, phenothiazines, lithium
Antiplatelet agents	Dipyridamole, phenindione
Biologics:	
Anti-CD-20	Obinutuzumab
Tumor necrosis factor (TNF)-α inhibitors	Infliximab, adalimumab, etanercept, abatacept
Tyrosine kinase inhibitors	Certolizumab, imatinib (Fig. 25.4)
Miscellaneous	Penicillamine, gold salts, statins, oral contraceptives, protease inhibitors, BCG, Hepatitis-B vaccines

Mucositis

It usually results from chemotherapeutic medication or chemoradiotherapy. Clinically, it begins with glistening erythema and feeling of soreness and eventually frank ulcers develop. Ulceration in immunocompromised patients may be severe leading to impaired mucosal barrier of oral cavity resulting in septicemia. Common drugs causing mucositis include agents such as 5-fluorouracil, methotrexate (Fig. 25.5), bleomycin, doxorubicin, melphalan and mercaptopurine.[1,26] Mucositis results from breakdown of the rapidly dividing mucosal epithelial cells leaving the mucosal tissue open to ulceration and infection, generation of free radicals and DNA damage.[27]

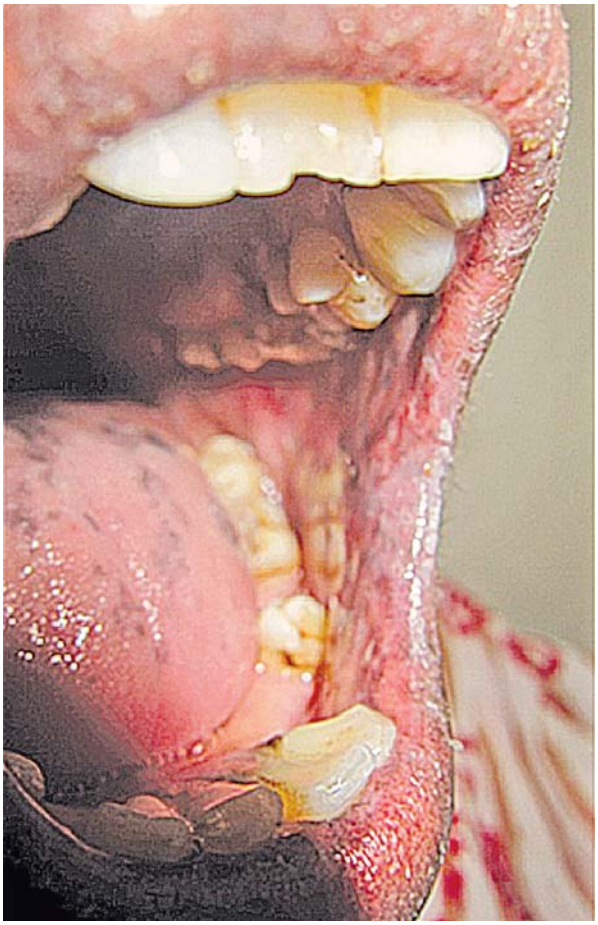


Fig. 25.4: Lichenoid lesions in oral cavity due to imatinib for CML. (Courtesy of Dr. Bela Shah, Ahmedabad.)

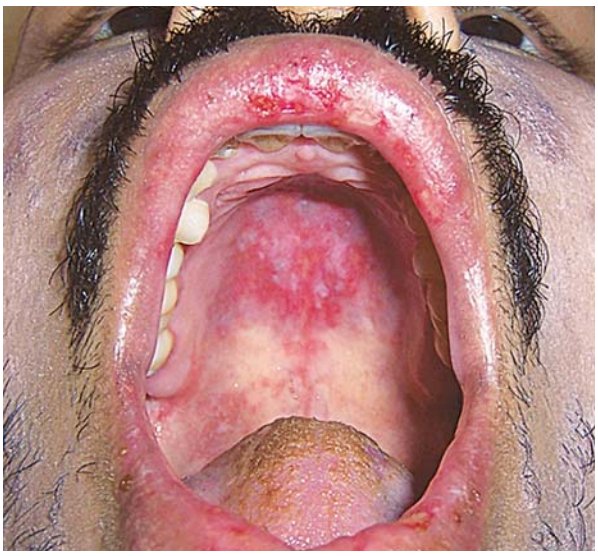


Fig. 25.5: Mucositis in a young patient on methotrexate.

Angioedema

The sudden swelling of lips and tongue following drug intake is not only aesthetically concerning but may sometimes result in an emergency in the form of laryngeal stridor. ACE inhibitors are most commonly implicated. The mechanism of angioedema to ACE inhibitor therapy is related to the kallikrein–kinin plasma effector pathway and failure of degradation of bradykinin, which is normally degraded by kininase II/ACE and bradykinin accumulates in tissues.[28] Drugs causing angioedema are ACE inhibitors, angiotensin receptor blockers (Fig. 25.6), calcium channel blockers (CCBs), antiplatelet drugs, cyclooxygenase inhibitors, hydrochlorothiazide, statins.[29–32]

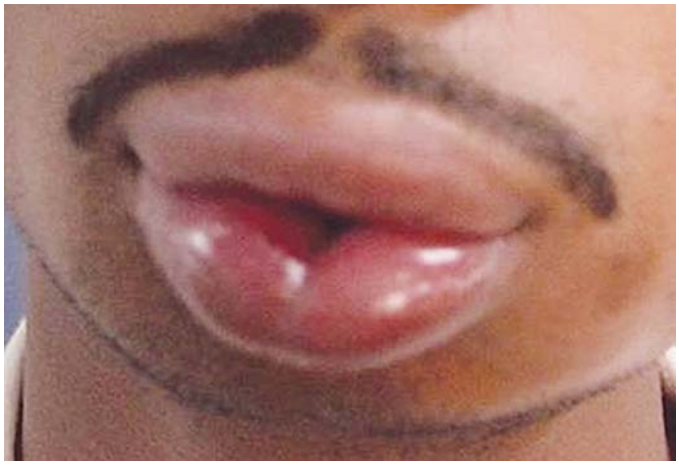


Fig. 25.6: Angioedema lips in a patient on ramipril for hypertension.

Pigmentation

Mucosal pigmentation may affect oral cavity alone or may be associated with pigmentation of skin and nails. Palate, tongue, buccal mucosa and gingiva in various combinations (Table 25.4) may be involved. Pigmentation in oral cavity may result from either or both of these mechanisms[1,26]:

1. **Deposition of pigments** in oral mucosa through chelation of iron and melanin with drug metabolites [antimalarials (Fig. 25. 7), tetracyclines, minocycline, clofazimine, imatinib]
2. **Stimulation of melanocytes** (chlorpromazine, amiodarone)

Pigmentation of tongue may also be due to black hairy tongue caused by staining from food and tobacco as a result of growth of pigment-producing bacteria that colonize the elongate filiform papillae. Black hairy tongue (Fig. 25.8) can be seen with the administration of oral antibiotics, corticosteroids, methyldopa, sulfonamides and excessive smoking in adults.[33]

Table 25.4: Drugs producing oral pigmentation and affection of site(s)

Mucosal site affected	Drugs
Palatal	Clofazimine Hydroxychloroquine Mepacrine Minocycline Quinacrine Tetracycline
Lingual	Zidovudine
Gingival	Oral contraceptive pills
Buccal and lingual	Cyclophosphamide Doxorubicin Docetaxel

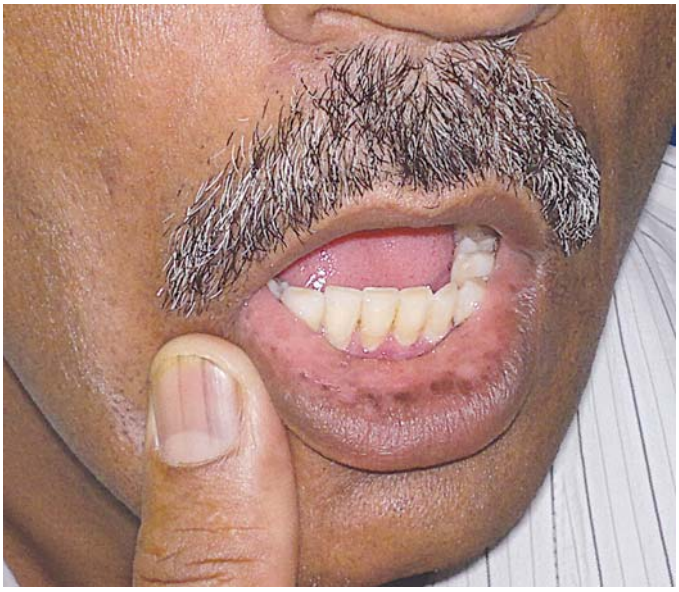


Fig. 25.7: Pigmentation on lips in a patient on long term chloroquine; note the associated pigmentation of nails.

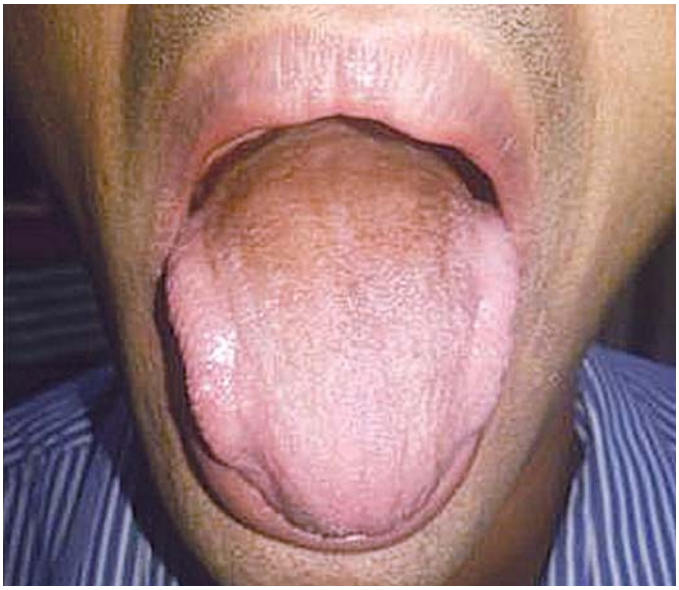


Fig. 25.8: Black hairy tongue in a patient taking linezolid.

Vesiculobullous Conditions

Various drugs may cause mucosal vesiculobullous lesions usually in association with cutaneous lesions, the presence of which make the diagnosis easier. Fixed drug eruption commonly affects mucosae. The other vesiculobullous drug reactions affecting oral cavity are lichen planus, erythema multiforme (EM), pemphigus vulgaris, lupus erythematosus (LE) and pemphigoid. The drug-induced lesions bear a close clinical, histopathologic and immunopathologic resemblance to idiopathic forms. The posterior buccal mucosa (cheeks), lateral borders of the tongue, and alveolar mucosa are most commonly involved. Lesions may be isolated, but bilaterally symmetric involvement is also not uncommon.[10]

Fixed Drug Eruption

FDE commonly affects oral mucosa (Figs. 25.9A and B); the lesions occur in isolation or may have lesions on skin and genitals as well (Fig. 25.9C). Clinical presentations of FDE may be bullous, erosions, sharply demarcated erythema or hyperpigmentation. The common culprit drugs include acetaminophen, NSAIDs, cotrimoxazole, tetracyclines, quinolones, imidazoles.[1,26] Table 25.5 shows drugs causing oral mucosal FDE.

Table 25.5 Drugs causing oral mucosal FDE and sites affected

Sites	Commonly implicated drugs
Tongue	Aminopyrine, amoxicillin, heroin
Palate	Fluconazole
Buccal mucosa	Azithromycin, tetracycline
Labial mucosa	Retinoids, ornidazole

Erythema Multiforme

EM, major or minor, can affect both the skin and mucous membranes and presents as irregular oral ulcers with diffuse erythema and target lesions of the skin. Lesions on skin have target/targetoid appearance and are commonly present on the acral parts. Hemorrhagic crusting on lips is characteristic (Fig. 25.10). Infections such as herpes simplex virus and mycoplasma pneumonia are more common causes than drugs, particularly in children.[34] Drug-induced EM represents approximately 25% of all reported cases.[35]

EM affecting skin and oral mucous membranes has been reported with adalimumab and infliximab.[36]

Drugs commonly causing EM include antibiotics (antimalarial, penicillin, sulfonamide and tetracycline), allopurinol, barbiturates, protease inhibitors, and NSAIDs.

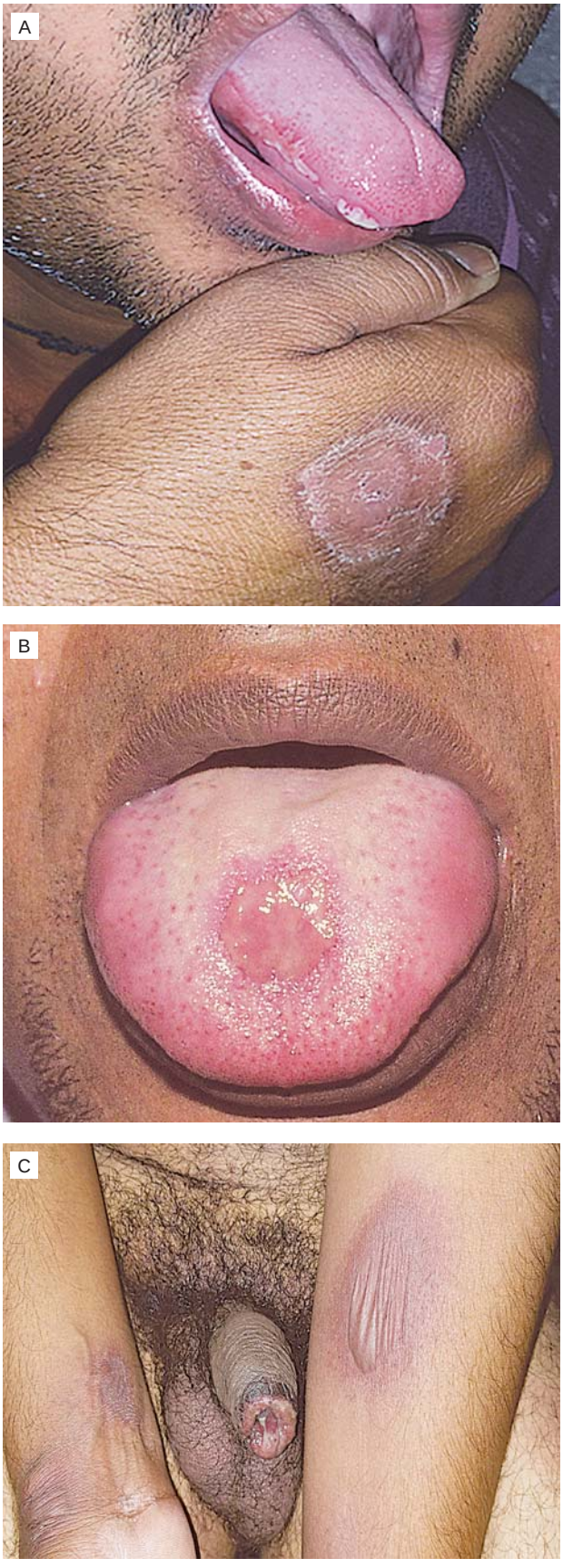
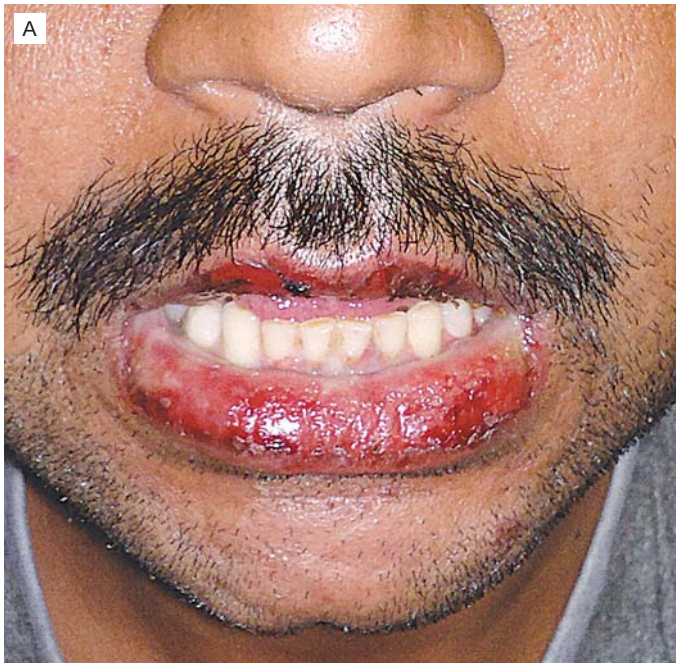


Fig. 25.9: (A) FDE lesions in oral cavity due to ornidazole; Also note the affection of hand; (B) FDE lesion on tongue (not a very common site of affection) due to metronidazole; (C) FDE affecting genital mucosa and forearms.



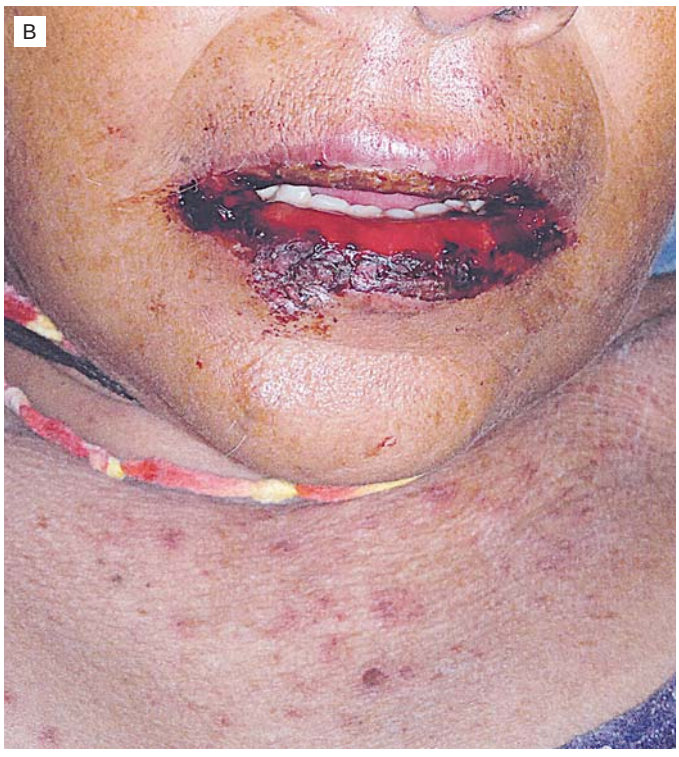


Fig. 25.10: (A & B) Lesions of erythema multiforme on lips and in oral cavity; note the characteristic hemorrhagic crusting.

SJS and TEN

SJS and TEN are life-threatening muco-cutaneous necrolytic diseases almost always affecting multiple mucosae, with oral mucosae being the most common site (Fig. 25.11). Unlike EM, they are much more commonly associated with use of medications. The drugs commonly implicated in SJS/TEN are listed in Table 25.6.[37]

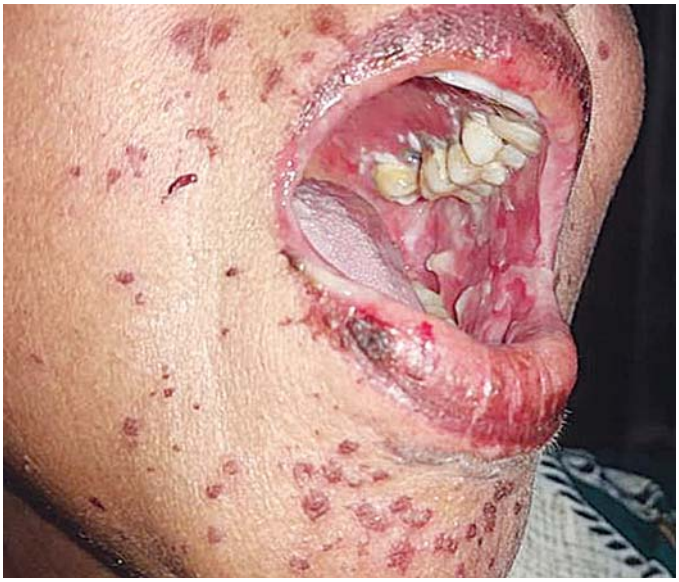


Fig. 25.11: Affection of oral cavity in SJS/TEN.

Table 25.6: Common drugs associated with SJS/TEN

Drug class	Associated drugs
Sulfonamide	Cotrimoxazole, sulfadoxine, sulfadiazine, Sulfasalazine
Anticonvulsants	Carbamazepine, barbiturates, phenytoin, lamotrigine, felbamate
Antivirals	Nevirapine, abacavir
Antibiotics	Cephalosporins, fluoroquinolones, vancomycin, aminopenicillins, doxycycline, erythromycin, ciprofloxacin
Uric acid lowering	Allopurinol
Antitubercular drugs	Thiacetazone, rifampicin, isoniazid, ethambutol
NSAID	Piroxicam, diclofenac, sulindac, ibuprofen, ketoprofen, naproxen, valdecoxib, celecoxib, rofecoxib

Pemphigus

Drugs can induce either pemphigus vulgaris or pemphigus foliaceus, although pemphigus foliaceus is uncommon in the oral cavity. Thiol-containing drugs are the most common cause of pemphigus-like reactions. The lesions in oral cavity are characterized by irregular ulcerations with ragged borders that may coalesce to involve large areas of the mucosa (Figs. 25.12 A and B). Patients may have circulating autoantibodies to the desmosomal components.[38]

Pemphigoid-like Reactions

Drug-induced pemphigoid-like reactions, may present as bullae, shallow erosions or desquamative gingivitis.

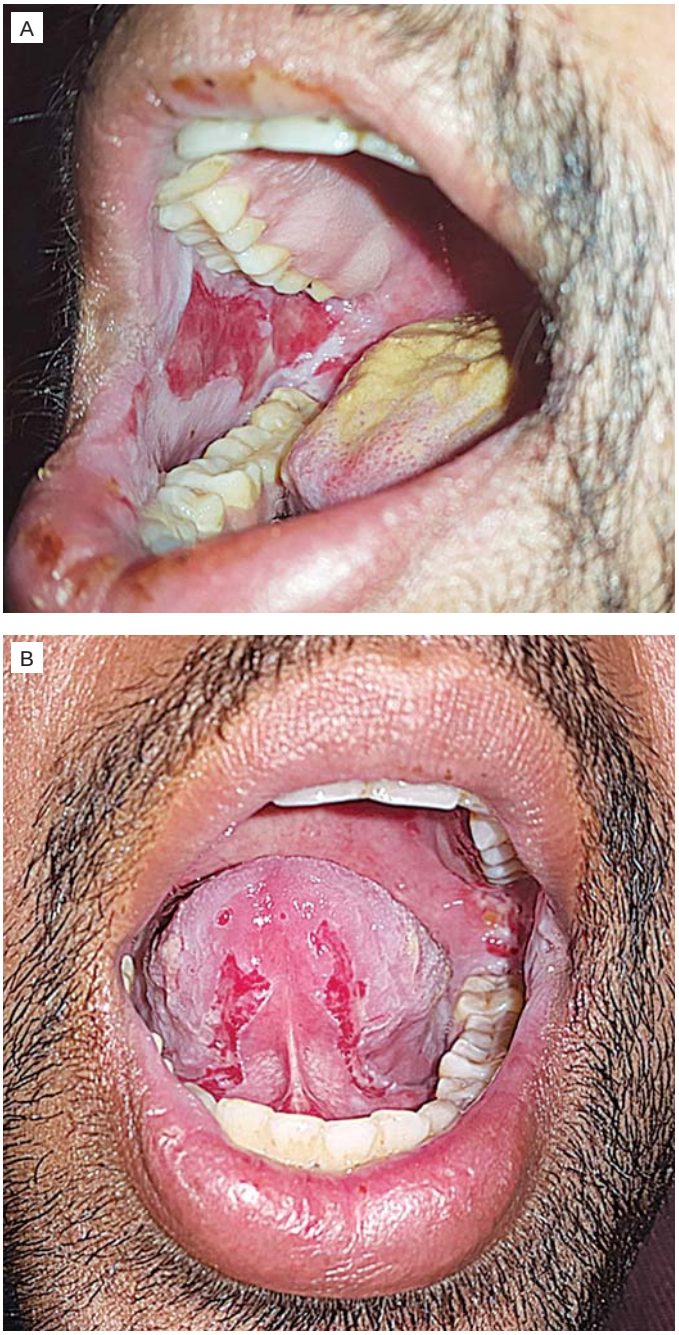


Fig. 25.12: (A) Lesions of pemphigus in oral cavity in a patient on anti-tubercular treatment, suspected to be due to rifampicin; (B) Pemphigus like oral lesions in a patient taking penicillamine.

Thiol-containing drugs and sulfonamide derivatives, NSAIDs, cardiovascular agents, antimicrobials, and anti-rheumatic agents are common agents implicated. Drug-induced pemphigoid may affect younger population and have more frequent oral involvement.[39]

Lupus Erythematosus

Drug-induced LE is most commonly associated with procainamide and hydralazine, although many other drugs such as hydantoins, isoniazid, lithium, methyldopa, penicillamine, procainamide, quinidine, carbamazepine, chlorpromazine, gold, griseofulvin among others have been implicated. Clinically, the oral lesions of drug-induced LE may simulate those of erosive LP, with irregular areas of erythema or ulceration bordered by radiating keratotic striae. These lesions may affect the palate, buccal mucosa, and gingival or alveolar tissues. The rarity of lichen planus on the hard palate may be helpful in differentiating it from drug induced LE.[40] The presence of characteristic cutaneous lesions of both conditions is also helpful in differentiating between LE and LP.

Osteonecrosis of Jaw

Osteonecrosis of jaw bone results from the temporary or permanent loss of blood supply to the bones and presents clinically as either exposed bone or a non-healing extraction socket. The other symptoms are swelling and loosening of teeth, altered local sensation, facial pain, toothache, recurrent infection, and marked oral odor.[41] This is a serious oral complication of treatment with bisphosphonates, most commonly zoledronic acid. Bisphosphonates have antiangiogenic properties and when used in conjunction with anti-vascular endothelial growth factor (VEGF) agents such as bevacizumab and sunitinib, the likelihood of osteonecrosis is enhanced.[42]

Malignancy

Although there have been reports of lymphoproliferative and squamous cell carcinoma (SCC) with immunosuppressants use, the evidence of development of malignancy in oral cavity is poor. However, there have been anecdotal reports of SCC developing in patients with oral LP treated with tacrolimus ointment.[43,44]

Hemorrhage

Drugs by affecting coagulation, vascular permeability, platelet number and functions may cause mucosal bleeding. Trauma may enhance the chances of bleeding. Drugs such as aspirin, NSAIDS, anticoagulants, chloramphenicol, penicillins, streptomycin, sulfonamides and chemotherapeutic agents may commonly cause oral bleeding. Spontaneous bleeding rarely occurs with platelet counts more than 20,000.[45] Decreased vitamin K levels resulting from use of broad spectrum antibiotics such as cephalosporins may lead to bleeding by altering the gastrointestinal flora and decreasing the absorption of vitamin K.[45]

GENITAL MADR

The genital mucosa is commonly affected by FDEs. In females, vulvar mucosa is more commonly involved than vaginal mucosa. In males, glans penis (Fig. 25.13) is most commonly affected followed by prepuce, shaft of penis and coronal sulcus. It may present as hyperpigmented macules, erythematous macules, maculo-ulcerative lesions, vesiculobullous lesions or ulcers. Other conditions affecting genital mucosa are SJS/TEN, vesiculobullous drug reactions and lichenoid drug reactions. Patient may have burning and itching sensation followed by erythematous plaque, vesiculation, bullae, erosions, and ulcers. The lesions may be commonly present on other mucosal sites and skin. The drugs causing genital mucosal lesions are usually the agents that affect oral mucosa. Interesting case of post-coital FDE affecting male genitalia has occurred in a male sensitive to cotrimoxazole from female partner using triple sulfa vaginal cream.[46] Another case of FDE to cotrimoxazole has been reported in the male partner after sexual intercourse with female partner who was taking cotrimoxazole; the male was sensitive to cotrimoxazole and developed FDE despite not taking the offending drug.[47] Localized argyria affecting vagina[48] and penile mucosa[49] has been reported with the long-term use of topical silver sulfadiazine. Penile ulcers have been reported after self-administration of subcutaneous papaverine for erectile dysfunction.[50]

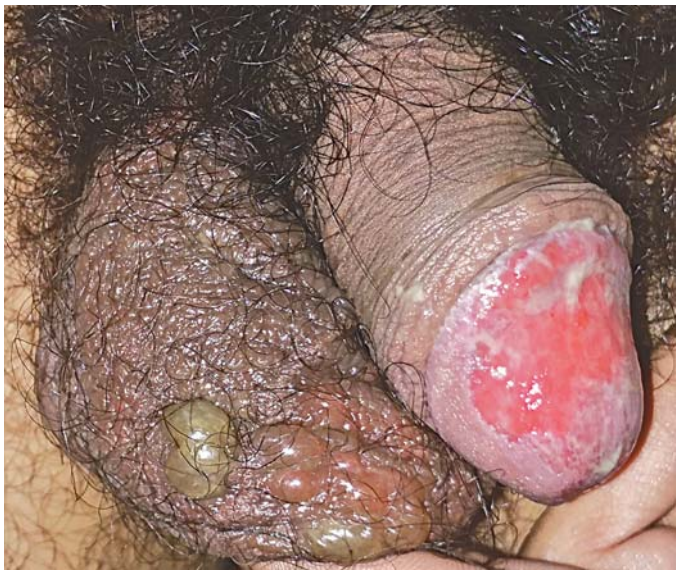


Fig. 25.13: Lesions of FDE on glans penis.

OCULAR MADR

Ocular mucosal affection by drugs usually manifests as pain, dryness, itching, redness, vesicles, bullae, erosions, and scarring. Ocular mucosa can be frequently involved in EM (Fig. 25.14 A) and drug-induced autoimmune bullous disorders. In SJS/TEN, ocular mucosal involvement (Fig. 25.14 B) is often the initial warning sign and may have significant sequelae if ocular care is neglected.

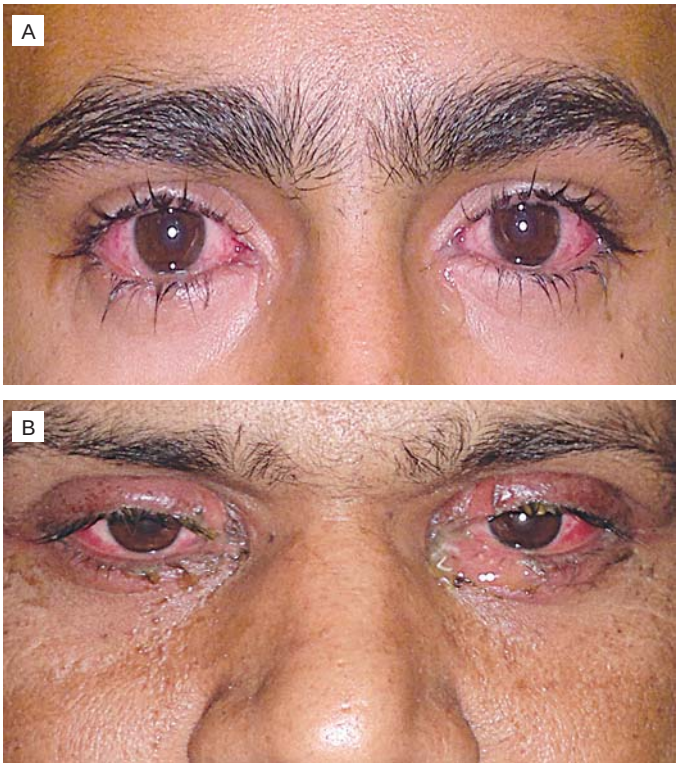


Fig. 25.14: (A) Ocular mucosal affection in a patient with Erythema multiforme; (B) Ocular mucosal affection in a patient with SJS/TEN.

Retinoids are widely used in dermatology and may have several ocular adverse effects; the most common ones are the dry eye syndrome and blepharoconjunctivitis. They occur in 20–50 % of patients taking the drug, usually 3–5 weeks after the initiation of the therapy.[51] Symptoms usually reverse completely on stopping the drug. Dry eye is caused by atrophic changes in meibomian glands as well as modification of the tear film composition. Patients may also complain of irritation in the eye and intolerance to contact lens.[51]

NSAIDs, another widely used class of drugs may cause conjunctivitis, keratitis, blurred vision, subconjunctival hemorrhage, besides causing SJS/TEN.[52] Methotrexate can cause periorbital edema, ocular pain, blurred vision, photophobia, conjunctivitis, blepharitis, decreased reflex tear secretion and non-arteritic ischemic optic neuropathy.[52] Biologics are now increasingly being used by dermatologists and may cause ocular adverse effects. Rituximab and abatacept have been reported to cause allergic conjunctivitis, eye pruritus, irritation, transient ocular edema, blurred vision, and visual impairment. Etanercept and infliximab

have been reported to paradoxically cause uveitis.[52] Mucous membrane pemphigoid (MMP) is a potentially serious autoimmune disease associated with skin and mucous membrane involvement including the oral cavity, esophagus, trachea and genitals besides ocular affection. Ocular manifestations of MMP can lead to blindness. Some medications that can cause drug-induced cicatrizing conjunctivitis (DICC) or pseudopemphigoid as a rare but serious adverse effect are adrenaline, demecarium bromide, dipivefrine, echothiophate iodide, idoxuridine, penicillamine, pilocarpine, practolol, thiabendazole, timolol and epinephrine eye drops.[53,54]

ANAL MADR

The anal mucosae may be involved in form of ulcers (nicorandil), FDE (cotrimoxazole, naproxen), and allergic contact dermatitis (antihemorrhoid drugs: calcium dobesilate and herbal preparations, lignocaine). The involvement of anal mucosa is relatively less frequent, accounting for 5% of all MADRs.[55]

AURAL

Involvement of aural mucosa of the middle ear through pathology extending from external auditory canal in its acute stages has been reported with acetaminophen-induced SJS/TEN.[56] Sildenafil has potential vasodilator side effect and has been associated with vestibular neuritis within 2 hours of taking oral medicine and presenting clinically as tinnitus in both the ears. This may probably happen because of mucosal inflammation of vasculopathic origin.[57]

NASAL

The serious drug-induced vesiculobullous conditions such as EM major, SJS/TEN may involve nasal mucosa in the form of erosions and hemorrhagic crusting and may cause difficulty in breathing. Obstruction of nasolacrimal duct may also result from ocular sequelae of purulent conjunctivitis, entropion/symblepharon/synechiae formation.[58]

TOPICAL MEDICAMENTS AND MADR

Mouth rinses, oral medicaments, swishes, ophthalmic drops, vaginal pessaries and anal suppositories may lead to MADRs. It usually presents as an acute irritant reaction (to aspirin, chlorhexidine, gentian violet, silver nitrate, sodium lauryl sulfate) or allergic contact reaction (to antibiotic lozenges, anesthetic agents, neomycin, bacitracin, mouthwashes, etc.).

Management of MADR

A high index of suspicion and thorough workup to elicit and eliminate the causative offender drug/agent is the most important aspect of management. Some of the other management essentials include:

- Maintaining mucosal hygiene by normal saline, chlorhexidine, povidone iodine wash and gargles. Mucosal care, particularly ocular is a very important part of management in conditions such as TEN/SJS and cicatricial pemphigoid and may lead to blindness if not managed promptly and properly.
- Agents to alleviate the pain e.g. lignocaine viscous, benzocaine in orabase, ice chips; systemic analgesics may be used if the pain is severe.
- Anti-inflammatory and immunosuppressive agents such as triamcinolone paste in orabase, tacrolimus ointment in oral lichenoid reaction.
- Folinic acid supplementation in suspected acute methotrexate toxicity.
- Specific systemic therapy if associated mucosal conditions are part of SCAR.

LEARNING ESSENTIALS

- A wide variety of drugs, both systemic and topical may affect mucosal sites; most common of which is oral mucosa.
- Mucosal reactions by drugs usually occurs in association with skin involvement, but may occur in isolation as well.
- Sometimes the mucosal affection by drugs may lead to permanent sequelae e.g. blindness in cases of SJS/TEN.
- Identifying and withdrawing the culprit drug (s), maintenance of oral hygiene, relieving pain, soft and bland diet, avoidance of smoking, tobacco chewing and alcohol are some of the practical therapeutic measures in MADR.

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Chapter

26

Drug-Induced Erythema Multiforme and Vasculitis

Rajeev Sharma • Tarang Goyal • Anupam Das

SUMMARY

- Erythema multiforme is an immunologically mediated hypersensitivity reaction.
- The two most significant precipitating agents include viral infections and drugs.
- Cutaneous vasculitis is a small-vessel vasculitis characterized by leukocyte infiltration, inflammation, and necrosis of vessel walls.
- Treatment includes discontinuation of the medication and use of immunosuppressive agents.

ERYTHEMA MULTIFORME

Introduction

Erythema multiforme (EM) was first identified in 1817 by Bateman. It was previously known by different names including *"Herpes Iris"* and *"erythema exsudativum multiforme"*. Vasculitis on the other hand, is an inflammation of blood vessels caused by varied etiological factors.

Etiopathogenesis

Erythema multiforme is an immunologically mediated hypersensitivity reaction characterized by influx of $CD8^+$ T lymphocytes leading to apoptosis of the keratinocytes.[1] The two most significant precipitating agents include viral infections (90% cases) and drugs (<10% cases). In virus-associated EM of which *herpes simplex virus* (HSV) is the commonest cause, there is predominance of interferon-γ in the lesions. However, in drug-induced cases, the lesions show abundance of tumor necrosis factor α.[2] The incidence is similar in males and females. Table 26.1 enumerates some common drugs causing EM.

Table 26.1: Drugs causing erythema multiforme[3,4]

Antibiotics/ Antibacterials	Penicillins, amoxicillin, cephalosporins, ciprofloxacin, azithromycin, clindamycin, sulfonamides
Anticonvulsants	Carbamazepine, phenytoin, barbiturates
Antifungals	Fluconazole, terbinafine, griseofulvin
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Ibuprofen, celecoxib, naproxen
Miscellaneous	Allopurinol, oral antidiabetics, furosemide, gold, protease inhibitors

Clinical Features

Drug-induced EM is preceded by history of intake of the drug and thus, the role of a meticulous history taking cannot be over-emphasized. There may be a prodromal phase of itching/burning prior to the appearance of lesions. To begin with, the lesions appear as erythematous macules over the dorsum of hands, extensors of extremities, palms (Fig. 26.1), soles and oral mucosa, which become papular in due course of time to finally evolve into a typical target lesion, characterized by a central dusky area, a paler pink or edematous zone and a peripheral reddish zone (Fig. 26.2). The edematous area may not be found in all cases.[5] Severe inflammation may lead to vesiculobullous lesions (Fig. 26.3) Oral lesions lead to significant deterioration in the quality of life. There may be painful ulceration, hemorrhagic crusting (Fig. 26.4) and odynophagia with or without

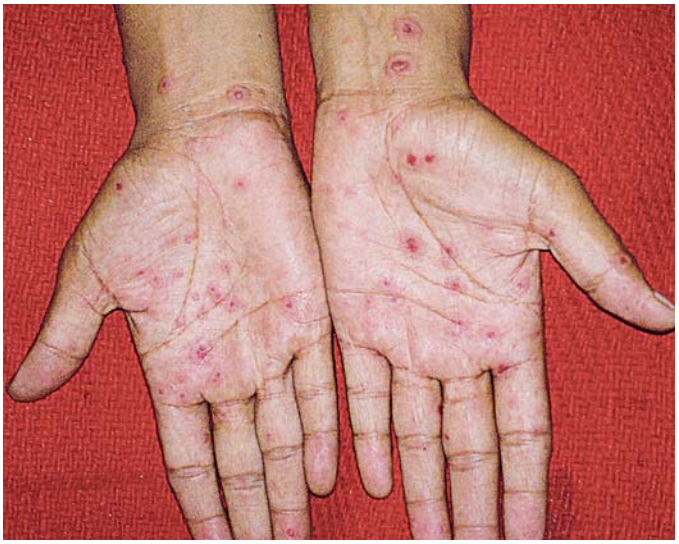

Fig. 26.1: Lesions of EM on palms; cotrimoxazole taken for acne was the suspected drug.

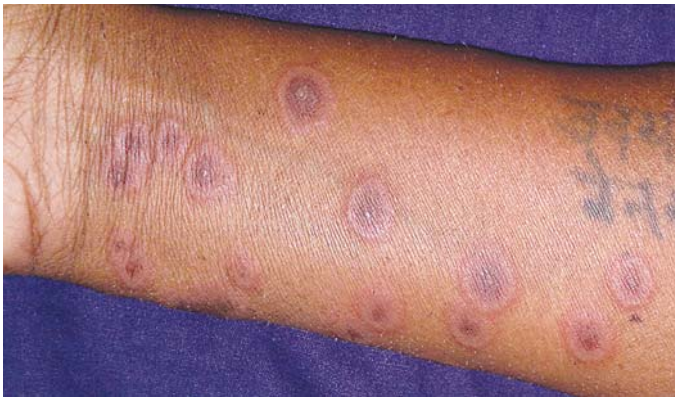

Fig. 26.2: Typical 3 ringed target lesions of EM. Carbamazepine was the suspected drug.

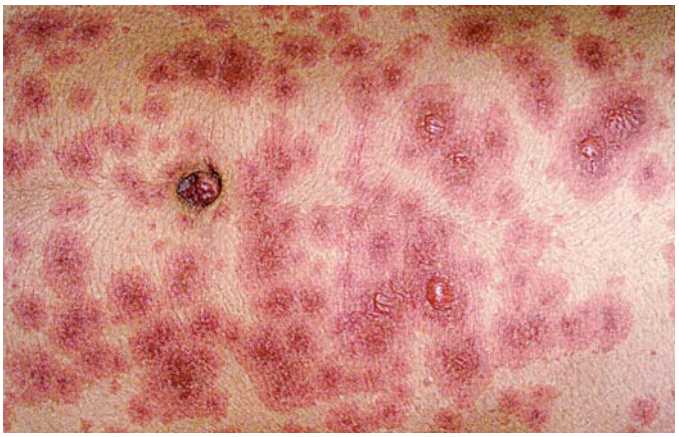

Fig. 26.3: Vesicular lesions in EM in a patient taking phenytoin.

lymphadenopathy. Ocular lesions (Fig. 26.5) lead to painful and obscured vision. In rare situations, there may be typical lesions of EM over the oral mucosa and lips, in the absence of any other cutaneous lesion. Such cases have named as "oral erythema multiforme."[6,7]

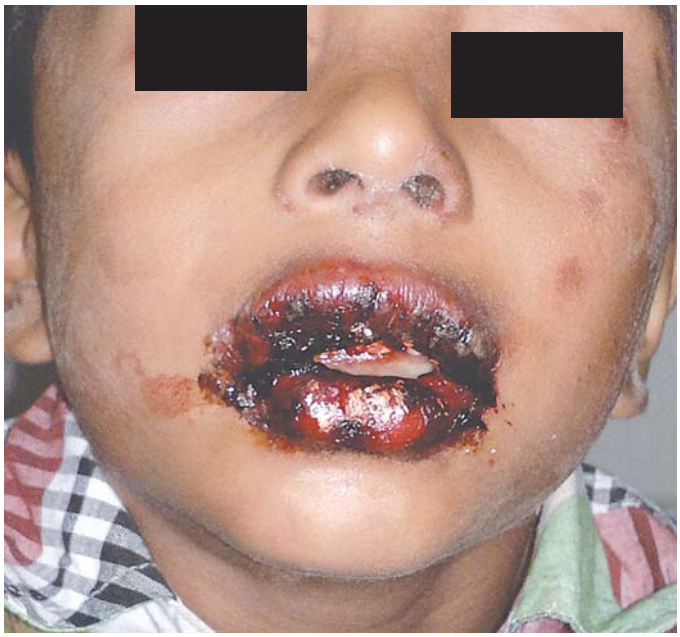

Fig. 26.4: Hemorrhagic crusting of lips, characteristic of EM.

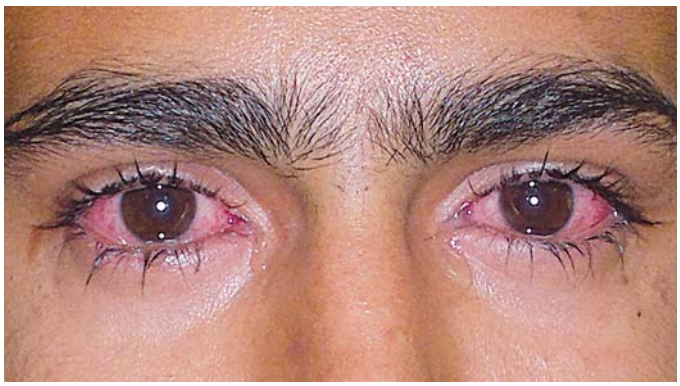

Fig. 26.5: Ocular mucosal affection in EM.

Workup

Diagnosis of the condition is mainly clinical, together with a good and detailed history of drug intake. The following features (Table 26.2), though not absolute, will aid in differentiating infective and drug induced EM.

Differential Diagnosis

Early EM may have to be distinguished from other dematoses like polymorphic light eruption, urticaria multiforme, urticarial vasculitis, pityriasis rosea, lupus erythematosus, vasculitis & figurate erythemas.

Treatment

Apart from discontinuation of the offending drug, mild cases may require only symptomatic treatment in form of oral antihistamines, analgesics, topical

zinc oxide, mild to moderately potent steroids, saline or antiseptic and anesthetic gargles. In severe cases fluid and nutritional support, ocular, genital and cutaneous wound care would be necessary. A short course of oral corticosteroids under cover of antibiotics if required may aid early recovery though evidence based studies are lacking.

Table 26.2: Differences between drug induced and viral erythema multiforme

Characteristics	Drug induced EM	Viral induced EM
Etiology	Drugs listed in Table 26.1	Mainly HSV1 & 2
Sites of Predilection	Face & acral extremities	Mainly acral extremities
Morphology of lesions	Polymorphic, target lesions uncommon. Vesiculo-bullous lesions may be present	Polymorphic, target lesions common
Constitutional symptoms	Usually present and may be severe	Usually not seen or may be mild
Course	Usually acute and self limited	Usually acute and self limited and follows an episode of clinical herpes. May have recurrence even without clinically evident episodes of preceding viral infections
Skin Biopsy	Keratinocytic necrosis mainly in acrosyringeal region, spongiosis, dermal edema less severe , perivascular lympho-histiocytic infiltrate mainly of CD8+ T lymphocytes	Focal necrotic keratinocytes, exocytosis, spongiosis, severe dermal edema, perivascular lympho-histiocytic infiltrate mainly of CD4+ T lymphocytes
Polymerase chain reaction (PCR)	Negative for herpes DNA	Positive for herpes DNA
Immunohisto-chemistry	Positive for TNF-α	Positive for IFN-ϒ

CUTANEOUS VASCULITIS

Introduction

Cutaneous vasculitis also called as hypersensitivity vasculitis or leucocytoclastic vasculitis (LCV) is a small-vessel vasculitis characterized by leukocyte infiltration, inflammation, and necrosis of vessel walls. Numerous conditions, including drug reactions, infections, connective tissue and autoimmune disorders, malignancies and ingestion of or exposure to foodstuffs and chemicals have been implicated in the development of LCV.[8–10]

Clinical Features

Drug-induced LCV accounts for approximately 10%–20% of all cases of cutaneous vasculitic diseases. Clinically, drug-induced vasculitis occurs in young females. Most commonly it presents as palpable purpura (Fig. 26.6). Lesions are usually round, 1–3 mm in diameter and barely palpable. Vesicles and bullae, urticaria and splinter hemorrhages may also be seen. The cutaneous lesions are often asymptomatic, although patients may report itching, burning or pain also. Table 26.3 lists some of the drugs causing vasculitis.

The diagnostic features of drug-induced vasculitis include age >16 years, use of possible offending

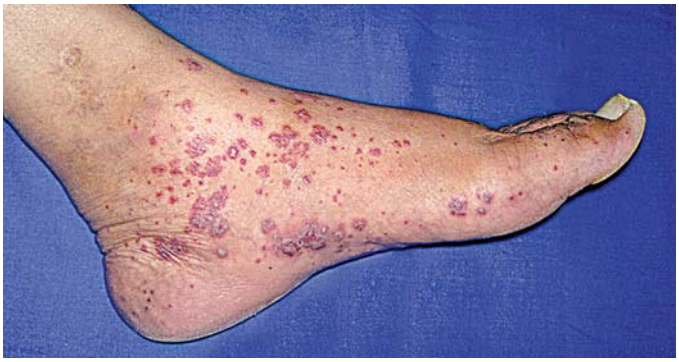

Fig. 26.6: Leucocytoclastic vasculitis with inflammatory palpable purpuric lesions around ankle.

Table 26.3: Drugs Causing Vasculitis

Antibiotics	Cefotaxime, minocycline, antithyroid drugs, benzylthio-uracil, carbimazole, methima-zole, propylthiouracil, trim-ethoprim-sulfamethoxazole, vancomycin
Antitumour necrosis factor- α agents	Adalimumab, etanercept, infliximab
Psychoactive agents	Clozapine, thioridazine
Miscellaneous drugs	Allopurinol, D-penicillamine, hydralazine, levamisole(particularly levamisole contaminated cocaine in drug abusers), phenytoin, sulfasalazine, orlistat, famciclovir

drugs in temporal relation to the symptoms, palpable purpura, maculopapular rash and biopsy of the skin showing neutrophils around an arteriole or venule.[11]

Systemic Involvement

Systemic involvement is considered to be present if there is clinical documentation of gastrointestinal involvement such as nausea, vomiting, diarrhea, blood in stools; renal involvement such as hematuria; rheumatologic presentations such as arthralgia and symptoms that cannot be explained by processes other than the patient's vasculitis.[12–14] Intra-alveolar hemorrhage is the most commonly reported pulmonary manifestation with consequent cough, dyspnea and hemoptysis. Systemic involvement is not common in drug-induced vasculitis if the inciting drug is withdrawn on time. The kidney is the most commonly involved organ and the renal features vary widely, including hematuria, proteinuria and elevated serum creatinine.

Work Up and Investigations

A detailed history should be obtained with past medical and drug records of at least 6 months prior to eruption. Although there are no specific laboratory findings, eosinophilic count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) are commonly elevated.

Routine Investigations

Complete blood cell count, ESR, CRP, blood chemistry panel, urine analysis, chest X-ray & fecal occult blood testing may be undertaken.

Histopathology

Biopsy specimens show angiocentric, segmental inflammation, endothelial cell swelling, and fibrinoid necrosis of blood vessel walls with infiltrate of neutrophils, lymphocytes, and eosinophils.

Serology

Patients with drug-induced vasculitis typically harbor antineutrophil cytoplasmic antibody (ANCA) directed at one or more neutrophil cytoplasmic antigens; the most common antigens being the granule proteins myeloperoxidase (MPO), human leucocyte elastase (HLE), cathepsin G, and lactoferrin. Table 26.4 shows various immunological markers in different types of drug-induced vasculitis.

Differential Diagnosis[11,16]

- Acute herpetic stomatitis
- Pemphigus vulgaris
- Bullous pemphigoid
- Paraneoplastic pemphigus
- Stevens Johnson syndrome
- Aphthous stomatitis
- Bullous lichen planus
- Fixed drug rash
- Anaphylactic stomatitis

Treatment

Treatment includes the discontinuation of the medication and immunosuppressive agents. Short course of systemic steroids are given. In moderate to severe cases, a dose of oral corticosteroids at 60–80 mg/day, tapered over 3–6 weeks can be given. In cases of persistent or very severe LCV, dapsone 100–150 mg per day in combination with immunosuppressive drugs such as cyclosporine (3–5 mg/kg per day) is a good option. Monitoring of serum ANCA surveillance for emergence of a chronic underlying vasculitis should be done. Rituximab use has been reported in various subsets of vasculitis patients, particularly those with ANCA-associated vasculitis. Drug-induced vasculitis has a better prognosis in comparison to idiopathic vasculitides.[15]

Table 26.4: Various laboratory markers and their importance to differentiate between drug-induced vasculitis, SLE, and ANCA-associated vasculitis

S. No	Laboratory markers	Drug-induced vasculitis	SLE	ANCA-associated vasculitis
1	Antihistone antibodies	Common	Rare	Absent
2	dsDNA	Absent	Common	Absent
3	Immune complex	Rare	Common	Absent
4	Antiphospholipid antibodies	Common	Common	Rare
5	ANCA	Common	Rare	Common

ANCA - antineutrophil cytoplasmic antibody; SLE - systemic lupus erythematosus.

LEARNING ESSENTIALS

- Drug-induced EM is preceded by a classical history of intake of the causative drug and thus, the role of a meticulous history taking cannot be over-emphasized.
- Drug-induced LCV accounts for approximately 10%–20% of all cases of cutaneous vasculitic diseases.
- In moderate to severe cases, a short course of oral corticosteroids can be given.
- Monitoring of serum ANCA surveillance for emergence of a chronic underlying vasculitis should be done.
- Drug-induced vasculitis has a better prognosis in comparison to idiopathic vasculitides.

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Chapter

27

Granulomatous Drug Reactions

Nidhi Shah • Roni P. Dodiuk-Gad • Neil H. Shear

SUMMARY

Granulomatous drug eruptions are rare and include 4 major types: Interstitial granulomatous drug reaction (IGDR), drug-induced accelerated rheumatoid nodulosis, drug-induced granuloma annulare (GA), and drug-induced sarcoidosis. IGDR and drug-induced GA are mostly localized to the skin, whereas both drug-induced accelerated rheumatoid nodulosis and drug-induced sarcoidosis may include major systemic involvement. In all 4 types, a temporal association between the initiation of drug therapy and appearance of lesions following drug intake and likewise clearance of lesions upon cessation of drug, and resolution after cessation of the implicated drug is characteristic. A prolonged time course between initiation and cessation of the drug, and the emergence and clearance of lesions, ranging from several weeks to months, makes the diagnosis of granulomatous drug eruptions and identification of the offending medication challenging. Most patients experience resolution, or at least improvement of symptoms, on discontinuing the medication. In cases of persistent or relapsing course, immunosuppressive treatment is needed. It is also reasonable to consider continuing the offending medication in skin-limited disease, especially if the drug has proved to be effective in treating a systemic disease, the risks and benefits have been assessed with the patient, and proper follow-up is conducted. Granulomatous drug eruptions should always be considered in the differential diagnosis of noninfectious granulomatous diseases of the skin, as awareness of this entity will avoid prolonged disease and unnecessary treatments.

INTRODUCTION

Granulomatous dermatitis may be defined as having an inflammatory cutaneous infiltrate in which cells of the mononuclear phagocyte system lineage i.e. histiocytes predominate. In most instances, these cells are aggregated into well-demarcated focal lesions called granulomas, although a looser, more diffuse arrangement may be found. There is usually an admixture of other cells, especially lymphocytes, plasma cells, and fibroblasts. The characteristics of a granuloma depend not only on the properties of the causative irritant but also greatly on host factors. The activated macrophages transform into epithelioid histiocytes and giant cells.[1] Non-infectious granulomatous diseases include granuloma annulare (GA), annular elastolytic giant cell granuloma, necrobiosis lipoidica, necrobiotic xanthogranuloma, interstitial granulomatous dermatitis, palisaded neutrophilic granulomatous dermatitis (PNGD), sarcoidosis, and metastatic Crohn's disease.[2] Granulomatous drug eruptions are a rare subgroup of noninfectious granulomatous diseases of the skin. We attempt to summarize current knowledge on the various types of granulomatous drug eruptions, which include the following types of reactions:

- Interstitial granulomatous drug reaction (IGDR), including the subtype drug-associated reversible granulomatous T-cell dyscrasia.
- Drug-induced accelerated rheumatoid nodulosis
- Drug-induced GA
- Drug-induced sarcoidosis
- Other granulomatous drug eruptions: Cutaneous granulomatous reaction to injectable drugs and vaccinations, photo-induced granulomatous eruption, and miscellaneous.

INTERSTITIAL GRANULOMATOUS DRUG REACTION

IGDR described by Magro and colleagues in 1998, is a rare entity of unknown prevalence, with a

peculiar histopathology, characterized by presence of histiocytes in the dermis, between fragmented collagen bundles, leading to the term IGDR.[3]

Etiopathogenesis

The list of drugs capable of inducing IGDR, which includes various groups, is increasing (Table 27.1). The pathogenesis is unknown. It has been proposed that the drug alters the antigenicity of dermal collagen and elicits an immune response.[10]

Table 27.1: Drugs that may induce an interstitial granulomatous drug reaction

- Calcium channel blockers*[3,4]
- ACE inhibitors[3]
- Lipid-lowering agents[3,5]
- Anti-tumor necrosis factor agents: Infliximab, adalimumab, etanercept, and lenalidomide[6,7]
- β-blockers[3]
- Tricyclic antidepressants[3]
- Histamine H2-receptor antagonists[3]
- Furosemide[3]
- Carbamazepine[3]
- Brompheniramine[3]
- Ganciclovir[8]
- Febuxostat[9]
- Anakinra[10]
- Trastuzumab[11]
- Darifenacin[12]
- Sennosides[13]
- Herbal medications[14,15]

* Most common

Clinical Presentation

The most common cutaneous features are symptomatic erythematous to violaceous annular plaques with a predilection for the flexures (intertriginous areas, medial thighs, and inner aspects of the arms),[3] and, occasionally, indurated borders and central clearing.[9,10] Other reported clinical presentations include generalized erythematous macules and papules[9,10]; erythroderma[4]; multiple tender, erythematous, violaceous, poorly demarcated, firm papules, and plaques on both palms and soles;[8,16] and erythema nodosum-like lesions.[14]

Lag Period

There may be a prolonged period between the initiation and cessation of the drug and the emergence and clearance of IGDR lesions, ranging from several weeks to months.[10] Twenty patients with IGDR in the study by Magro and colleagues[3] had ingested the offending drugs from 4 weeks to 25 years (average, 5 years) before the onset of the eruption.

Differential Diagnosis

The erythematous or violaceous plaques in the area of skin folds may mimic the scaly plaques of mycosis fungoides (cutaneous T-cell lymphoma). The differential diagnosis also includes erythema anulare centrifugum, lupus erythematosus, pigmented purpura, lichen planus, dermatomyositis, macular GA,[2] and interstitial granulomatous dermatitis with arthritis (Ackerman syndrome).[17]

Systemic Associations

Characteristically, there is no systemic association in IGDR.[3]

Evaluation and Management

The clinical and histological findings must be correlated for the diagnosis of this entity.[3] A temporal association between the initiation of drug therapy and appearance of lesions and resolution after the cessation of the implicated drug is characteristic. However, the diagnosis may be challenging because of the prolonged time lapse between the initiation of drug and appearance of lesions and resolution of lesions following stoppage of the offending drug, ranging from several weeks to months.[5] In many cases, the lesions resolve on discontinuation of the drug and reappear on reintroduction of the drug.[5]

Histology

IGDRs have variable histologic presentations. Microscopically, they typically exhibit a diffuse interstitial infiltrate of lymphocytes and histiocytes with elastic and collagen fiber fragmentation, vacuolar interface dermatitis, and scant to absent mucin deposition.[18] Tissue eosinophilia is present in most cases.[3] Of note, some 50% of cases exhibit atypical lymphocytes with hyperchromatic convoluted nuclei, found either in the interstitium or along the dermoepidermal junction, with variable epidermotropism.[3] The clinical and histopathological appearances of IGDR and the granulomatous slack skin variant of cutaneous T-cell lymphoma are strikingly similar: Both present as violaceous plaques in intertriginous areas and show elastolysis, tissue eosinophilia, and granulomatous infiltrates with atypical lymphocytes. In IGDR, however, typical intraepidermal cells do not include Sezary cells and

do not exceed the atypia of the dermal component, findings typical of granulomatous slack skin. Other features supporting the diagnosis of IGDR are hypersensitivity reactions, such as papillary dermal edema, vesiculation, basilar vasculopathy, and dyskeratosis.[3]

Treatment

Complete resolution of the lesions usually follows the withdrawal of the causative medication.[3] Awareness of this will avoid prolonged disease and unnecessary treatments. In cases where IGDR does not resolve in several months, repeat biopsy is recommended to exclude granulomatous slack skin, and should include gene rearrangement studies.[2] Histopathology suggesting malignancy will require further investigation.[19] The prolonged time lapse between the initial ingestion of the offending agent and the onset of cutaneous findings and polypharmacy may further complicate the identification of the culprit.[19] In the study by Magro and colleagues, 15 of 20 patients with IGDR[3] had 1 or more of the implicated drugs discontinued, and the eruption resolved within 1 to 40 weeks (mean, 8 weeks) in 14 patients with improvement, although no complete resolution was seen in 1 patient. No recurrences developed at a 12-month follow-up. In the cases of IGDR induced by anti-tumor necrosis factor (TNF) medications, it is recommended that all patients undergo a careful workup to rule out an infectious process.[6]

A distinct subset of the IGDR is drug-associated reversible granulomatous T-cell dyscrasia, characterized by atypical T-lymphocytic infiltrates that manifest a light microscopic, phenotypic, and molecular profile that closely parallels cutaneous T-cell lymphoma but regresses when the causal drug is withdrawn. The cutaneous findings include persistent eczematous papules, plaques, or patches, or infiltrative plaque-like lesions, often in flexures of the skin, which usually resolve following discontinuation of the offending drug in 2 weeks to 10 months. One patient continued to have a peripheral blood monoclonal T-cell population despite the absence of skin lesions, indicating the importance of drug modulation to prevent the conversion of what is initially a reversible T-cell dyscrasia to one that may become irreversible.[20]

DRUG-INDUCED ACCELERATED RHEUMATOID NODULOSIS

Etiopathogenesis

Kremer and Lee[21] first noted accelerated rheumatoid nodulosis in 1986 during a study of long-term methotrexate (MTX) therapy for rheumatoid arthritis (RA). In 2001, Ahmed and colleagues[22] termed this acceleration MTX-induced accelerated rheumatoid nodulosis (MIARN). Other medications have been implicated in accelerated rheumatoid nodulosis (Table 27.2). However, as MTX is the most common drug to be associated with this condition,[19,23] this section focuses on MIARN. A double-blind study that compared MTX and azathioprine in patients with refractory RA showed an 8% incidence of MIARN with MTX (with arthritic involvement) and none with erythematosus.[24] Other collagen vascular diseases besides RA were associated with MTX induced accelerated rheumatoid nodulosis, including juvenile RA,[25] psoriatic arthritis,[34] and systemic lupus erythematosus.[35] Although the mechanism of accelerated nodulosis is unclear, studies have suggested a genetic etiology or, at least, predisposition.[22,36] HLA-DRB1*0401 and RF seropositivity have been associated with MIARN.[22] A 2007 cross-sectional study identified a polymorphism of the methionine synthase reductase gene in RA patients that was increased in these patients in comparison with the general population and was associated with MIARN.[36]

Clinical Presentation

Clinical presentation of MIARN includes multiple flesh-colored to erythematous indurated papules and nodules. MIARN affects mainly the hands, usually the metacarpophalangeal and proximal interphalangeal joints,[17,22–24] although other locations have been reported including knees, heel pads, achilles tendons, arms, elbows, thighs, shoulder girdle, buttocks, and feet.[25,26] The nodules are typically painful, but discomfort is minimal in most patients.[22]

Rheumatoid nodulosis has been reported with other drugs (Table 27.2).

Table 27.2: Drugs implicated in accelerated rheumatoid nodulosis

- Methotrexate[22–26]
- Anti-TNF agents: Etanercept,[27] adalimumab,[28] infliximab[29]
- Aromatase inhibitors: Letrozole[30]
- Azathioprine[31,32]
- Leflunomide[33]

Lag Period

Nodule formation is not related to cumulative MTX dosage. The duration of MTX therapy reported before MIARN ranges widely from hours to months.[22,23,25,26]

The lag period reported with medications other than MTX that induce accelerated rheumatoid nodulosis ranges from 1–26 months.[27–33]

Differential Diagnosis

Differentiation from classic rheumatoid nodules and rheumatoid nodulosis may be challenging. MIARN is characterized by multiple lesions that disappear with termination of MTX and do not recur in previously affected areas in the absence of MTX therapy. The differential diagnosis also includes pseudorheumatoid nodules,[19] cutaneous extravascular necrotizing granuloma of Churg–Strauss, and rheumatoid neutrophilic dermatitis.[23]

Systemic Associations

One patient in the report by Ahmed and colleagues[22] developed lung disease with biopsy proven intrapulmonary nodules that resolved completely after MTX withdrawal. Another patient developed extensive cutaneous nodulosis associated with new cardiac murmurs of aortic and tricuspid regurgitation. Other reported organ involvement includes the lungs,[37] heart,[38] and brain.[39]

Histology

Nodules have a histology similar to that of rheumatoid nodules[22]: Multinodular foci of massive necrobiosis with adjacent scarring in soft tissue or subcutaneous fat, surrounded by a histiocytic palisade, with fibrin deposition, often seen with rosettes of histiocytes surrounding collagen bundles in the reticular dermis.

Treatment

MIARN often regresses with discontinuation of MTX and reappears once MTX is restarted.[22] Ahmed and colleagues reported that nodules regressed within 6.1 ± 4.5 months when MTX was discontinued but persisted for 41.2 ± 14.9 months when MTX was continued.[22] The addition of hydroxychloroquine, etanercept, D-colchicine, and penicillamine have been shown to accelerate healing in cases where MTX was continued.[22,25,40] Discontinuation of MTX and aggressive intervention may be warranted with development of symptoms, ulceration, infection, or mechanical issues.[19,25]

In the cases of accelerated rheumatoid nodulosis induced by drugs other than MTX, treatment included discontinuation of the offending drug,[30] changing the dosage of the offending drug,[28] adding an immunosuppressive drug,[27] and not changing or adding any treatment.[29]

DRUG-INDUCED GA

Etiopathogenesis

GA is a benign, self-limited cutaneous inflammatory condition of unknown etiology.[2] The first association between GA and drugs was reported in 1980 with gold,[41] since then various drugs have been implicated in its etiology (Table 27.3). The pathogenesis of drug-induced GA is not known, although the possible role of immune dysregulation induced by immunosuppressive drugs has been suggested.[44] Several cases of TNF-α antagonists inducing GA have been reported,[42] a curious finding given that TNF-α inhibitors can be used for the treatment of refractory GA.[44]

Table 27.3: Drugs that induce GA

- Anti-TNF agents: Infliximab, adalimumab, etanercept, thalidomide[42,43]
- Pegylated interferon-α[44,45]
- Amlodipine[46]
- Gold[41,47]
- Allopurinol[48]
- Topiramate[49]
- Paroxetine (photoinduced GA)[50]
- Diclofenac[51]
- Immunizations: Hepatitis B and anti-tetanus vaccination[52,53]
- Intranasal calcitonin[54]
- Desensitization injections[55]

Clinical Presentation

Various clinical presentations of drug-induced GA have been reported with different drugs, with the generalized type being the most common.[42,45,46,48,52] Gold has been reported to induce papular GA.[41,47] A case series study assessed 199 patients with RA and 127 with spondyloarthropathies, treated with anti-TNF antagonists.[42] Nine (4.5%) cases of GA were identified in the group of patients with RA; 2 treated with infliximab, 6 with adalimumab, and 1 with etanercept. No patient with spondyloarthropathies developed such skin lesions. In 7 patients the skin eruptions developed during the first year of anti-TNF treatment, and in 2 patients during the second year. All 9 patients developed a generalized type of GA located mostly on the hands, forearms, and fingers.[42] Thalidomide has been reported to induce GA presenting as a violaceous, ring-like, firm papular eruption localized on the dorsal aspect of both hands 15 days after starting the treatment of multiple

myeloma with thalidomide.[43] GA, photo-induced by paroxetine has been reported following 1 year of treatment and confirmed by photobiological study.[50]

Systemic Associations

There was no systemic involvement with any of the drugs except for the case of GA induced by amlodipine, whereby the patient developed a transient fever within 10 days of starting the drug. Three days after the febrile episode, the patient developed bilateral ankle edema with a rash on the lower legs.[46]

Evaluation and Management

The association between GA and a drug is considered when lesions: (1) appear after the initiation of the drug; (2) resolve after the discontinuation of the drug; (3) reappear with the resumption of the drug in the same area and with similar characteristics; and (4) have histology characteristic of GA.[49]

The histological findings of drug-induced GA are palisading granulomas, collagen degeneration, mucin, and a lymphohistiocytic infiltrate. The presence of mucin is the key histological feature that distinguishes GA from other non-infectious granulomatous diseases.[56]

In most cases the lesions regress with discontinuation of the offending drug.[46–49] However, it may be decided to continue the medication after explaining the risks and benefits and obtaining the patient's consent. In a case series of 9 patients with RA who developed generalized granuloma due to anti-TNF treatment, only 2 had to stop the anti-TNF therapy because of the extent of skin lesions whereas the other 7 responded well to local corticosteroid therapy, with resolution of the lesions without discontinuing the treatment.[42]

DRUG-INDUCED SARCOIDOSIS

Etiopathogenesis

Sarcoidosis is an autoimmune disease of unknown origin characterized by the presence of noncaseating epithelioid cell granulomas in multiple organs. Proposed causes include infections, environmental agents, and autoantigens, but to date no specific etiologic agent has been identified. Genetic and immunologic factors are thought to play an important role in the development of the disease through increased susceptibility to antigenic stimulation.[2]

Various drugs have been reported to induce cutaneous sarcoidosis (Table 27.4), and several theories suggested to explain the pathogenesis of this process.[2] In 1987, Abdi and colleagues[57] reported the first case of histologically proven sarcoidosis in a woman treated with interferon (IFN)-α. The role of IFN-α in the induction of sarcoidosis is probably related to its capacity to induce a predominant Th-1 immune response, which is considered the main immunologic event in granuloma formation.[58] Sarcoidosis has been effectively treated with TNF-α blockers, owing to the important role of TNF-α in granuloma formation and maintenance.[70] However, there have also been case reports of an unexpected, paradoxic effect of the development of sarcoidosis in patients on anti-TNF-α therapy.[62–64,71] Most cases of sarcoidosis developing on TNF-α therapy involved organs other than skin, although cases of only cutaneous sarcoidosis have been reported.[62] In a retrospective case review assessing 34 cases of sarcoidosis that developed during anti-TNF therapy,[63] cutaneous sarcoidosis was documented in 32% of cases. Although the cause of sarcoidosis with anti-TNF therapy is not known, several mechanisms have been postulated: Cytokine imbalance secondary to TNF-α suppression;[62] modification of the pathways of p38 kinase and adenosine A2A and A3 receptors in CD4 cells-biochemical modifications that unbalance the activity of CD4 cells, in particular Th-17, which may contribute to the generation of granulomatous processes such as sarcoidosis;[71] genetic variation of the TNF-α and polymorphism of the genes that mediate cytokine production may determine predisposition.[64]

Table 27.4: Drugs causing cutaneous sarcoidosis

- Interferon-α[57–61]
- Anti-TNF agents: Etanercept, infliximab, adalimumab[62–64]
- Ipilimumab (a monoclonal antibody directed against cytotoxic T-lymphocyte antigen-4)[65]
- Hyaluronic acid injection[66]
- Ophthalmic drops containing sodium bisulfite[67]
- Zinc[68]
- Desensitization injections[69]

Clinical Presentation

Cutaneous involvement in sarcoidosis may be either specific (noncaseating granulomas) or nonspecific (reactive processes), and both have been observed in patients with drug-induced sarcoidosis.[62–64] In a retrospective case review assessing 34 cases of sarcoidosis developing during anti-TNF therapy,[63] the most common clinical sign of cutaneous sarcoidosis was erythema nodosum-like lesions; the average time between the initiation of therapy and onset of symptoms in this study was 22 months. In a report on exacerbation of recalcitrant cutaneous sarcoidosis with adalimumab,[64] the cutaneous lesions of

sarcoidosis became more erythematous, infiltrated, and ulcerated, and associated with retroauricular adenopathies following the third injection. The cutaneous manifestation of sarcoidosis-like reaction associated with ipilimumab[65] included grouped erythematous papules, some in a linear array, in a patient with stage IIIC melanoma following the second dose of high-dose ipilimumab 10 mg/kg. In a review of the literature on cutaneous signs of IFN-α induced sarcoidosis,[60] skin involvement was documented in 56% of the reports. Symptoms appeared from 1 to 6 months after drug intake and skin lesions usually took the form of erythema nodosum, subcutaneous nodules, plaques, and scars.

In an assessment of sarcoidosis among 68 patients with chronic hepatitis C virus (HCV) infection,[58] a temporal relationship between initiation of antiviral therapy and diagnosis of sarcoidosis was found in 47 cases. The sarcoidosis appeared during the first 6 months after commencing antiviral therapy in 31 of 47 (66%) patients, between 6 and 12 months in 9 (19%), and after 12 months in the remaining 7 (15%). In 8 cases, the initiation of antiviral therapy for HCV reactivated preexisting sarcoidosis. The clinical picture of sarcoidosis in these 47 cases included predominantly pulmonary and cutaneous features. Thirty (60%) patients presented with cutaneous involvement, including painful subcutaneous nodules in 16 cases, plaques in 8, erythema nodosum in 6, and exanthema in 1. The main sites of cutaneous sarcoidosis were the arms in 13 patients, legs in 9, knees in 7, head in 6, and neck in 3. In 4 patients, cutaneous lesions appeared adjacent to older scars or tattoos. In the 2 cases of IFN-α–induced sarcoidosis koebnerized along venous drainage lines,[59] painless, firm, erythematous skin papules developed in a linear distribution along the cephalic and median antebrachial veins of both forearms in former areas of drug injections. In a report of sarcoidal foreign body granulomatous dermatitis associated with ophthalmic drops,[67] multiple brown-black asymptomatic papules were described over the chin, involving nasal mucosa and columella. Hyaluronic acid injections have been reported to induce cutaneous sarcoidosis: tender nodules in both nasolabial folds that developed 4 months after the injection.[66]

Systemic Associations

Drug-induced sarcoidosis may involve only the skin or present as a multisystem disease that includes cutaneous involvement.[63,65,66,71] In the case of sarcoidosis-like reaction associated with ipilimumab, shortness of breath and hypoxemia requiring oxygen supplementation, were signs of pulmonary involvement in addition to the cutaneous manifestations.[65] In a review of the literature on cutaneous signs of IFN-α-induced sarcoidosis,[60] non-specific respiratory symptoms were noted in 54% and mediastinal lymphadenopathy in 50% of the patients. Many cases of sarcoidosis developing while on anti-TNF therapy involve organs other than the skin,[71] with lung and surrounding lymph nodes, the most commonly affected.[63] Other organs include liver, eyes, salivary glands, central nervous system, joints, kidneys, and bone marrow.[61,63] In the case of IFN-α-induced sarcoidosis: Since systemic symptoms of sarcoidosis (e.g. fatigue, pulmonary dysfunction, arthromyalgias, adenopathies) mimic the side effects of the antiviral therapy, special attention to dermatologic signs may offer a clue to an early diagnosis of IFN-induced sarcoidosis.[60]

Evaluation and Management

The diagnosis of drug-induced sarcoidosis is established when clinical findings are supported by histologic evidence.[58] The histological findings of drug-induced sarcoidosis are similar to those of sarcoidosis and include classically naked tubercles (granulomas), which are characterized by dermal, noncaseating, epithelioid, histiocytic granulomas; multinucleated giant cells; and lack of an additional extensive inflammatory infiltrate.[19] Most patients experience resolution, or at least improvement of symptoms, on discontinuing the medication,[63] a relatively mild course of disease in contrast to the natural history of sarcoidosis in general.[61] Few cases of persistent or relapsing course require immunosuppressive treatment.[63,65,66] In a retrospective case review assessing 34 cases of sarcoidosis developing during anti-TNF therapy,[63] the primary treatment for 33 of the 34 cases was discontinuation of the TNF-inhibitor therapy. A small number of patients were treated with systemic corticosteroids and antituberculosis medications. Complete clearance of disease was reported in 33 of the 34 cases, with a mean time of 5.2 months for clearance after the discontinuation of the TNF inhibitor. In a retrospective study of 60 cases of sarcoidosis induced by IFN-α,[61] management of the disease consisted of discontinuation of IFN-α either alone or in combination with corticosteroid administration. Most patients experienced resolution or, at least, improvement of symptoms. The few (11%) who had a persistent or relapsing course needed additional immunosuppressive treatment. However, caution should be exercised with systemic steroids, when sarcoidosis is associated with treatment for HCV as it may increase the viral load. In the case of IFN-α-induced cutaneous sarcoidosis koebnerized along venous drainage lines,[59] because there was no systemic involvement the IFN and ribavirin therapy were continued for a total of 48 weeks, after which the skin lesions spontaneously disappeared.

OTHER GRANULOMATOUS DRUG ERUPTIONS

Other granulomatous drug eruptions have been reported, including cutaneous granulomatous reaction to injectable drugs[72] and vaccinations,[73] photo-induced granulomatous eruption by hydroxyurea,[74] and a characteristic drug eruption secondary to granulocyte colony-stimulating factor (G-CSF) whereby patients presented with an eruption 1 day to 3 weeks after the administration of this medication.[75] An interesting and previously unreported association was published recently on 2 patients with melanoma who developed cutaneous granulomatous eruptions during targeted BRAF inhibitor therapy.[76] In case one, after 2 months of treatment with dabrafenib and trametinib (MEK inhibitor), a papular eruption appeared, and concern regarding the progression of the disease prompted cessation of treatment. After the histopathologic diagnosis of granulomas, the patient was treated with clobetasol ointment, with resolution within days and resumption of therapy. In case two, after 5 months of vemurafenib treatment, the patient developed a granulomatous eruption that resolved 3 weeks after cessation of therapy. It is interesting that in case one, the histology revealed melanoma cells central to the granulomatous reaction, suggesting that the reaction was incited by the melanoma cells. The authors propose that in this case, granuloma formation represents immune activation toward possible melanoma regression, and therefore it is unnecessary to discontinue the therapy.

LEARNING ESSENTIALS

- Granulomatous drug eruptions are a rare entity and may present in various forms.
- May result paradoxically from the drugs used to treat some of these granulomatous eruptions.
- Decision to continue medications depends on the risk benefit assessment.
- Ruling out tuberculosis is important in the endemic setting, particularly where anti-TNF therapy is the presumed cause.
- Lag period from ingestion of drug to onset of rash can be prolonged.
- In some situations, addition of another agent to suppress the reaction may help continue the drug that may be needed.

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Chapter

28

Miscellaneous Drug Reactions

(Spongiotic Drug Reaction Pattern, Panniculitis Including Erythema Nodosum, Sweet's Syndrome, Lymphoma, Collagen Vascular Diseases, Pseudoporphyria, Pseudoscleroderma)

Tarang Goyal • Anupam Varshney

SUMMARY

- Drugs are a cause of reaction patterns and presentations in dermatology.
- They may begin immediately to few weeks or even 1 year after starting the drug.
- The reactions such as pseudoporphyria, systemic lupus erythematosus, scleroderma, pseudolymphoma simulate the systemic presentation, and a high index of suspicion is necessary to diagnose them.
- Histopathology and immunofluorescence should be performed to establish the diagnosis wherever feasible.
- Withdrawal of offending drug is of utmost importance for treating these otherwise treatment resistant cases.

INTRODUCTION

Drug eruptions are common adverse reactions to drug therapy. Although any drug is a potential cause of an adverse cutaneous reaction, some drugs are implicated more commonly than others in causing these reactions and are unpredictable in most cases. Histologically, the drugs can elicit a variety of inflammatory disease patterns in the skin, with no pattern being specific for a particular drug. Clinicopathological correlation should be established for relevant patterns, and withdrawal of inciting drug is of utmost importance in treatment of the patient. This chapter discusses some uncommon, yet important miscellaneous reaction patterns elicited by drugs. Many of these have significant systemic associations and share a close clinical resemblance to their idiopathic counterparts.

SPONGIOTIC DRUG REACTION PATTERN

Introduction

Eczematous rash as a broad group is a difficult condition for a dermatologist to classify except as a morphologic pattern because the cause is elusive in most cases. Drugs have been reported to induce or aggravate a wide variety of eczematous eruptions which clinically could be either of the well defined endogenous or exogenous variants. A crisp description of spongiform reactions to drugs has been mentioned to occur in several different clinical and pathogenetic settings.[1] A delayed hypersensitivity response is usually the underlying cause in most cases. Some of the drugs implicated in the common clinical forms of dermatitis are mentioned in Table 28.1.

Clinical Features

Clinically spongiotic drug reactions may manifest as an aggravation of an endogenous dermatitis like nummular eczema, atopic dermatitis, seborrheic dermatitis and even asteatotic dermatitis of the elderly. They are not an infrequent cause of local and systemic allergic contact reactions. The latter can be caused by administration of an allergen to an individual who has been sensitized to that agent by previous contact with it or with a related substance. Manifestations include exacerbation of vesicular hand dermatitis, flare at previously positive patch test site, or a systemic eruption involving buttocks, genital areas, flexures and skin folds like axillae, eyelids, elbows and side of the neck also known as "baboon syndrome". Other dermatoses like pityriasis rosea like eruption, phototoxic and photoallergic reactions may also be drug related.

Table 28.1: Drugs causing spongiotic drug reaction pattern

Type of Dermatitis	Common drugs implicated
Nummular dermatitis	Antimycobacterial drugs, latanoprost eye drops, ribavirin, mercury (in dental fillings), methyldopa, gold
Seborrheic dermatitis	Chlorpromazine, cimetidine, gold, arsenic, methyldopa
Atopic dermatitis	Infliximab
Allergic contact dermatitis	Topical antihistamines, corticosteroids, mupirocin, neomycin, NSAIDs, phenylenediamine, benzocaine, doxepin, fluorouracil, tea-tree oil
Systemic contact dermatitis	Aminophylline, amoxicillin, ampicillin, minoxidil, cimetidine, diuretics, erythromycin, gentamicin, hydroxyurea, hypoglycemic agents, immunoglobulins, isoniazid, neomycin, roxithromycin, thiamine, zinc in dental fillings
Photoallergic dermatitis	Alprazolam, amlodipine, chlordiazepoxide, chlorpromazine, diphenhydramine, griseofulvin, ibuprofen, ketoprofen, lomefloxacin, piroxicam, pyridoxine, ranitidine, sulfonamides, tetracyclines, thiazides
Phototoxic dermatitis	Carbamazepine, doxycycline, NSAIDs, ofloxacin, phenothiazines, retinoids, sulfonamides, thiazide
Nonspecific dermatitis	NSAIDs, ACE inhibitors, calcium channel blockers, thiazide diuretics, allopurinol, atenolol, amlodipine, estrogen, progesterone, etanercept, fluoxetine, gold, immunoglobulin infusion, infliximab, nifedipine, phenytoin sodium, heparin, and vitamin K

NSAID - non steroidal anti-inflammatory drug; ACE - angiotensin converting enzyme.

Adapted from Weedon et al.[1]

Diagnosis

It is very difficult to diagnose spongiform drug eruption without strong clinical suspicion. Biopsy will show epidermal spongiosis and in addition characteristic presence of exocytosis of lymphocytes and eosinophils. Exocytosis is out of proportion to the amount of spongiosis in the region. Other epidermal changes in spongiotic drug reactions include variable parakeratosis & acanthosis. The dermal infiltrate may extend into the mid dermis, not a feature of other spongiotic disorders.

Treatment

If a drug is suspected to cause the eruption, an improvement is expected to occur within a few days once it is withdrawn. This however may not be true for some drugs like gold, which can produce an eczematous eruption that may last for up to 12 months after the cessation of treatment. Symptomatic treatment including topical corticosteroids, topical calcineurin inhibitors, oral antihistamines and at times a short course of systemic corticosteroids may be given.

DRUG-INDUCED PANNICULITIS

Introduction

Between the well-known and recognized causative factors of panniculitides, infections, physical agents, autoimmune mechanisms, and neoplastic disorders are quite common. Drugs as inducers of panniculitides are seldom considered, with their report limited to anecdotal observations often without histopathological support.[2,3]

The causative relationship between drugs and panniculitis may be demonstrated by the history of previous drug intake and by clinical improvement after drug discontinuation.

Erythema nodosum is the most frequently reported drug-induced panniculitis. Drug-induced lobular and mixed panniculitides, including eosinophilic panniculitis, are even more rarely described (Table 28.2).

Post-steroid panniculitis[4] is a known but rare entity. It is a complication of systemic corticosteroid therapy mainly presenting in children. Clinically, it is characterized by multiple, erythematous, subcutaneous nodules or indurated plaques developing 1–35 days after rapid tapering or complete cessation of systemic steroid therapy, which was being used for rheumatic fever, nephrotic syndrome, leukemia, recurrent brain glioma, etc. requiring long-term systemic corticosteroids. Histologically, it presents as lobular panniculitis with mixed inflammatory infiltrates without vasculitis. Needle-shaped clefts within adipocytes are characteristic.

Trastuzumab[5] is a relatively new drug that has been introduced for metastatic breast cancer overexpressing human epidermal growth factor

Table 28.2: Drugs causing panniculitis and erythema nodosum

Erythema nodosum	Minocycline, oral contraceptives, sulfonamides, bromides, iodides, penicillin, phenytoin, nitrofurantoin, D-penicillamine, isotretinoin, thalidomide, hepatitis B vaccine, interleukin 2, aminopyrine, gold salts
Lobular and mixed panniculitides	Glatiramer acetate, interferon beta and heparin (at sites of injections), systemic steroids, tyrosine kinase inhibitors, vemurafenib, imatinib, dasatinib, aspartame
Necrotizing granulomatous panniculitis	Trastuzumab

receptor 2 (HER 2). Special mention here is necessary as it has known to be causing a rare cytoplasmic antineutrophilic cytoplasmic antibody necrotizing granulomatous panniculitis.

Recently, panniculitis with lipid crystallization at the site of etanercept injection[6] has been reported.

Clinical Features

Erythema nodosum (the most common presentation) is characterized by tender, subcutaneous, erythematous nodules, which are usually located on the anterior portion of the legs (Fig. 28.1). Clinical description of post-steroid panniculitis has been described earlier.

Treatment

Withdrawal of the drug, if possible, is a must. Nonsteroidal anti-inflammatory drugs and topical glucocorticosteroids are used for mild reactions. Systemic glucocorticosteroids may be required in patients with widespread involvement or more severe systemic symptoms. Rechallenge may lead to reappearance of lesions.

DRUG-INDUCED SWEET'S SYNDROME

Introduction

Sweet's syndrome (SS), also known as acute febrile neutrophilic dermatosis, is characterized by painful erythematous plaques on face and upper extremities, pathologic findings including fever, neutrophilia, and a diffuse infiltrate consisting predominantly of mature neutrophils that are typically located in the upper dermis. SS presents in three settings: classical (idiopathic), malignancy-associated, and drug-induced SS. Su and Liu[7] have proposed a set of diagnostic criteria for SS. They suggest that both major and two of four minor criteria must be met before diagnosing SS. The two major criteria are (1) the abrupt onset of tender or painful plaques or nodules and (2) histopathologically, a dense neutrophilic dermal infiltration without vasculitis.

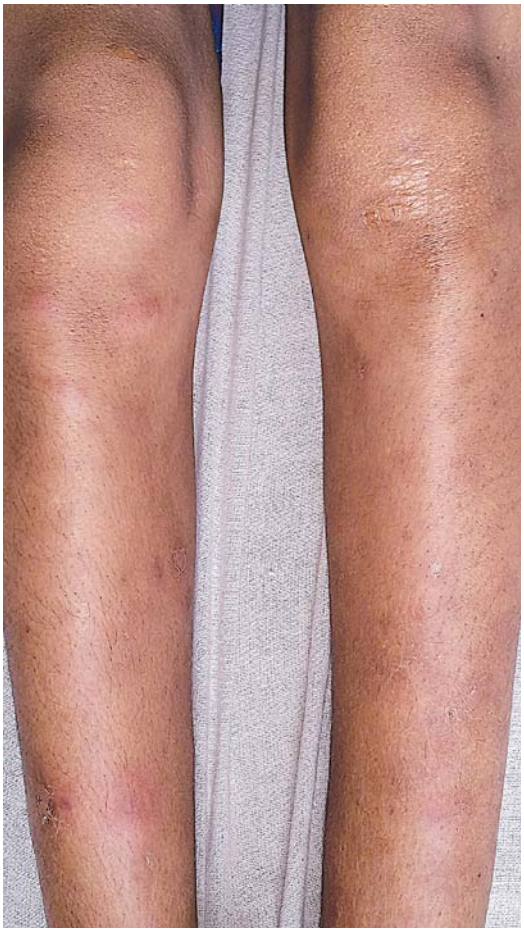


Fig. 28.1: Tender, erythematous, subcutaneous, nodules over legs due to oral contraceptive pills.

The four minor criteria are (1) a preceding fever or infection, underlying malignancy, inflammatory disease, vaccination, and pregnancy; (2) constitutional manifestations, including fever (>38°C), arthralgias, conjunctivitis; (3) a leukocytosis of >8000 cells/mm^3, >70% neutrophils; and (4) a good response to corticosteroids but not to antibiotics.

In 1989, von den Driesch[8] suggested that an elevated erythrocyte sedimentation rate should be added to the list of minor criteria.

Drugs have been found to cause SS in >5% of cases and are thus an uncommon cause of same.[9]

All-*trans*-retinoic acid, granulocyte colony-stimulating factor (G-CSF), celecoxib, hydralazine, nitrofurantoin, minocycline, oral contraceptives, lithium and

trimethoprim-sulfamethoxazole, bortezomib, imatinib mesylate have all been implicated (Table 28.3).

Table 28.3: Some common drugs implicated in causing Sweet's syndrome

Retinoids	All-*trans*-retinoic acid
	13-*cis*-retinoic acid
NSAIDs	Celecoxib
	Diclofenac
Contraceptives	Levonorgestrel/ethinyl estradiol
	Levonorgestrel-releasing intrauterine system
Colony-stimulating factors	Granulocyte colony-stimulating factor
	Granulocyte-macrophage colony-stimulating factor (Fig. 28.2)
	Pegfilgrastim
Antineoplastics	Bortezomib
	Lenalidomide
	Imatinib mesylate (Fig. 28.3)
	Hypomethylating agents (azacitidine, decitabine)
Antibiotics	Minocycline
	Nitrofurantoin
	Norfloxacin/ofloxacin
	Trimethoprim–sulfamethoxazole
Immunomodulator	Lenalidomide (Revlimid)
Miscellaneous	Furosemide, propylthiouracil, clozapine, carbamazepine, diazepam, abacavir, hydralazine

Pathogenesis

Significantly elevated levels of helper T-cell type 1 cytokines [interleukin 2 (IL2) and interferon-gamma] and normal levels of a helper T-cell type 2 cytokine (IL-4) were observed in the immunohistochemical studies of serum of patients with SS. Cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon-gamma, IL-1, IL-3, IL-6, and IL-8 are potential cytokine candidates, the levels of which are found to be raised in drug-induced SS. Recently, an X-inactivation assay to detect clonal restriction of neutrophils, based on the human androgen receptor (*HUMARA*) gene, was performed on SS skin biopsy specimens from four patients with acute myelogenous leukemia and two patients without underlying hematologic dyscrasia. But in cases of drug-induced SS this still need to be studied.

Clinical Features

Fever, painful erythematous plaques on face and upper extremities are present (Figs. 28.2 and 28.3). The peripheral blood eosinophilia seen in typical SS is typically absent in drug-induced SS as hematopoietic growth factors, which are implicated as the most common cause of drug-induced SS, are used to reverse chemotherapy-induced neutropenia.

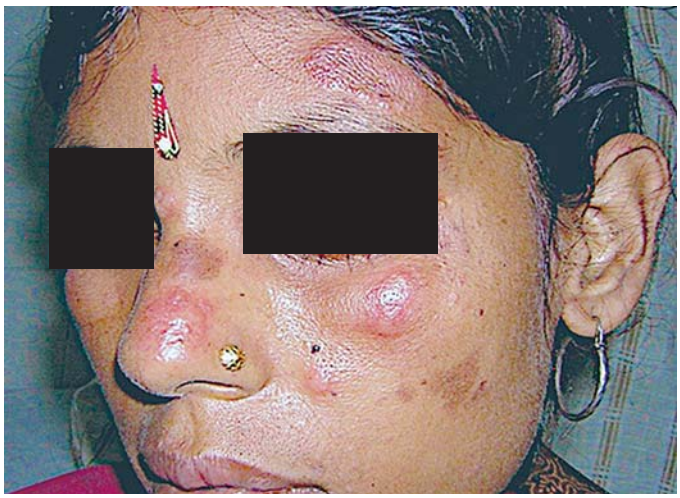


Fig. 28.2: Succulent, tender, erythematous plaques over face in Sweet's syndrome suspected due to imatinib.

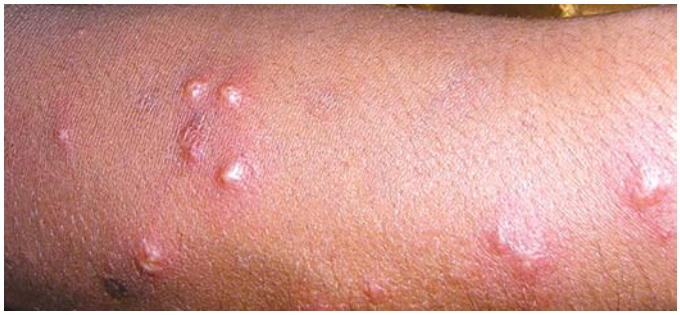


Fig. 28.3: Tender, erythematous pustulo-nodular lesions over forearms in Sweet's syndrome due to Granulocyte monocyte-colony stimulating factor GM-CSF in a neutropenic leukemic patient.

Diagnosis

Walker and Cohen established the criterion for drug-induced SS in 1996. They proposed two additional criteria for this variant, which are as follows:

1. Temporal association between drug ingestion and clinical appearance of lesions or recurrence with oral rechallenge.
2. Resolution of lesions with drug withdrawal or treatment with oral corticosteroids.

They further stated that both major criteria previously stated by Su and Liu, one minor criterion of pyrexia >38°C plus those two above stated major criteria (total of five criteria) are essential in establishing the diagnosis of drug-induced SS.

History of drug usage 1-3 weeks prior to appearance of lesions is often present.

Diffuse inflammatory infiltrate of neutrophils in the dermis, subcutaneous fat, or both without vasculitis is seen on biopsy.

Treatment

The offending drug should be removed immediately. Lesions usually disappear within 3–30 days. Topical application of high potency corticosteroids or intralesional corticosteroids may be effective for treating localized lesions. Systemic corticosteroids are the "gold standard" of therapy for SS. Other first-line oral systemic agents are potassium iodide and colchicine. Second-line oral systemic agents include indomethacin, clofazimine, cyclosporine, and dapsone.

DRUG-INDUCED LUPUS ERYTHEMATOSUS

Introduction

Drug-induced lupus erythematosus (DILE)[10,11] is a syndrome resembling mild idiopathic systemic lupus erythematosus (SLE) that resolves within days to months after withdrawal of the offending drug in a patient with no underlying immune system dysfunction characteristic of SLE. It presents with one or more features of classic SLE such as fever, weight loss, arthralgia, myalgia, pericarditis or pleuropulmonary inflammation. Drug-induced subacute cutaneous lupus erythematosus (DISCLE) was first described in 1985 with hydrochlorothiazide therapy in five patients. It is a DILE variant with predominant skin involvement (Figs. 28.4 through 28.6). A number of drugs have been implicated in inducing drug-induced LE, the most common being hydralazine, procainamide, quinidine, isoniazid, diltiazem, and minocycline (Box 28.1).

Box 28.1: Drugs implicated as a cause of LE/SCLE

Thiazides, piroxicam, D-penicillamine, sulfonylureas, oxprenolol, griseofulvin, terbinafine (Figs. 28.4 A–C), naproxen, aldactone, diltiazem, cinnarizine, captopril, cilazapril, verapamil, nifedipine, interferon beta, ranitidine, isoniazid, hydralazine, quinidine, methyldopa, procainamide, and atenolol

Biologics: Interleukins (e.g., IL-2), interferons (e.g., alpha, beta, gamma), tumor necrosis factor alpha inhibitors (etanercept, infliximab, adalimumab), and rituximab

Biologics such as ILs (e.g., IL-2), interferons (e.g., alpha, gamma, beta), and tumor necrosis factor alpha (TNF-α) inhibitors are associated with musculoskeletal symptoms and antibody production suggestive of a lupus-like autoimmune disorder.

Pathogenesis

Although the pathogenesis of DILE is not completely understood, a genetic predisposition may play a role, as has been shown with certain drugs metabolized by acetylation, such as procainamide or hydralazine. In SLE, the molecular mimicry is responsible for autoantibody production, whereas in DILE, autoantibodies are thought to be generated by a mechanism other than molecular mimicry.[12] Of several

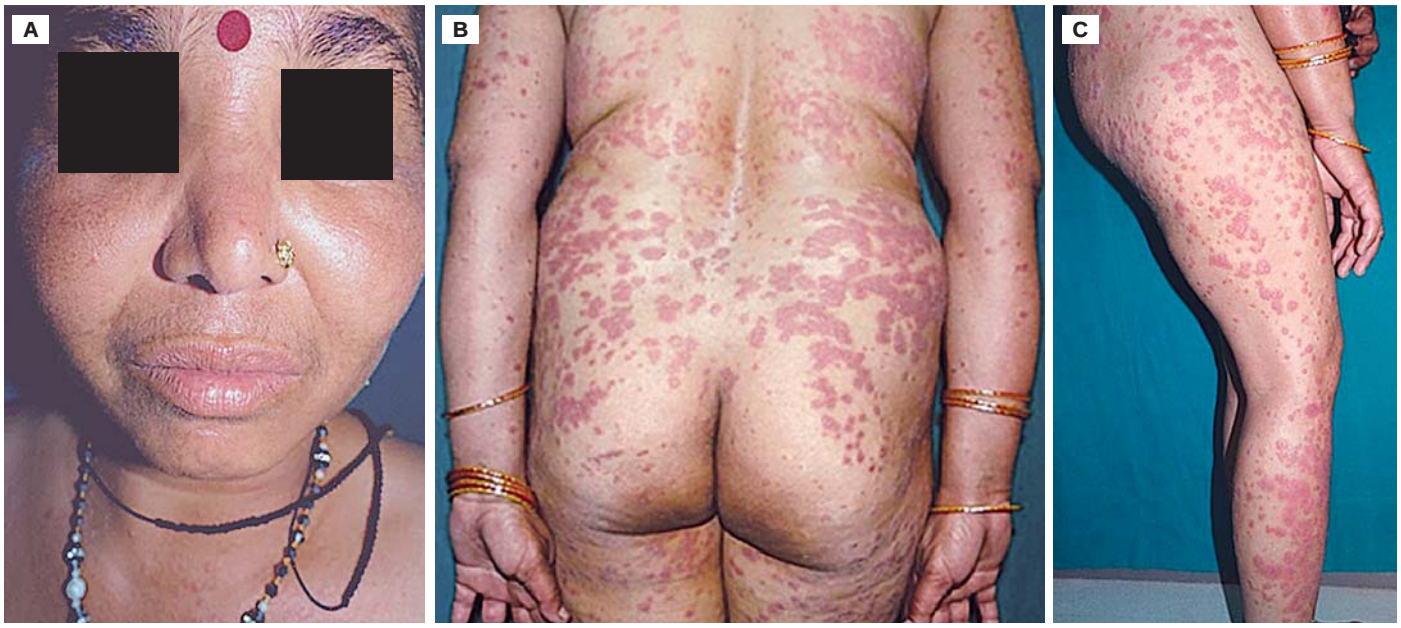


Fig. 28.4: (A) Malar rash in drug induced lupus suspected to be due to terbinafine; (B) The lesions of LE on trunk and buttocks in the same patient; (C) LE lesions on lower extremities.

proposed mechanisms, one is that the metabolites of the drug are subjected to oxidative metabolism and serve as a substrate for myeloperoxidase, which causes the formation of reactive metabolites that directly affect lymphocyte function in the thymus, disrupting central T-cell tolerance to the patient's own tissues and producing autoimmune T cells against them. A second theory is that with decreased T-cell methylation, an overexpression of lymphocyte function–associated antigen (LFA-1) occurs. T cells with hypomethylated DNA become autoreactive and cause antibody formation.

Clinical Features

The following criteria have been proposed for diagnosis:

1. No history suggestive of SLE.
2. Positive antinuclear antibody and at least one clinical feature of SLE.
3. Improvement in clinical and laboratory features after drug discontinuation.

   Usually it requires 3 weeks to 2 years of drug exposure before the appearance of symptoms.

The skin manifestations when present in classic drug-induced lupus show malar erythema, photoeruptions, and discoid and erythema multiforme–like lesions. As a rule, patients with DILE do not have mucosal ulcerations and alopecia.

Generally, the absence of central nervous system (CNS) and renal involvement is more suggestive of DILE than that of SLE. An exception is hydralazine-induced glomerulonephritis where rare cases of deaths have been reported. DISCLE differs from idiopathic SCLE in absence of visceral manifestations, frequent occurrence of malar rash, vasculitic manifestations, and bullous and erythema multiforme–like lesions. It is highly associated anti-Ro antibody (less frequently anti-La antibody) and shows a correlation with human leukocyte antigen (HLA-DR3 and/or HLA-DR2), as in idiopathic SCLE.

Diagnosis

Strong clinical suspicion as the symptoms appear a year after the drug was initiated.

The most important laboratory feature for drug-induced LE is an elevated anti nuclear antibody (ANA) titer, mostly with a homogeneous staining pattern corresponding to the presence of anti-histone antibodies, typically with exclusion of the broader array of autoantibodies characteristic of SLE. These anti-histone antibodies are usually present in >95% of cases. Typically, antibodies to dsDNA are not present.

In cases of minocycline-induced LE,[13] antibodies to antineutrophil cytoplasmic antibodies (ANCA) are present. ANA and anti-Ro and/or anti-La antibodies are also found in the majority of drug-induced SCLE cases if human tissue substrate is used.

Treatment

The condition usually, but not always, resolves after the withdrawal of the causative drug. The clinical symptoms resolve within 4–12 weeks. However, antibodies may persist till 6–12 months.

DRUG-INDUCED PSEUDOPORPHYRIA

Introduction

Pseudoporphyria is a photosensitive blistering disorder with clinical and histological features identical to porphyria cutanea tarda (PCT), but which lacks serum and urine porphyrin abnormalities.[14,15] Medications, chronic renal failure including dialysis, excessive sun exposure, tanning beds, and UVA radiations have all been reported to cause pseudoporphyria. Drugs causing pseudoporphyria are listed in Table 28.4.

Table 28.4: Drugs causing pseudoporphyria

NSAIDs	Naproxen[16], nabumetone, oxaprozin, ketoprofen, mefenamic acid, sulbactam
Antibiotics	Nalidixic acid, tetracycline, ampicillin–sulbactam
Diuretics	Chlorthalidone, bumetanide, furosemide, hydrochlorothiazide/triamterene
Retinoids	Isotretinoin, etretinate
Miscellaneous	UVA tanning beds, PUVA, UV light, cyclosporine, 5-fluorouracil, pyridoxine, amiodarone, flutamide, dapsone

NSAIDs - nonsteroidal anti-inflammatory drugs; UV - ultraviolet; PUVA - psoralen and ultraviolet A.

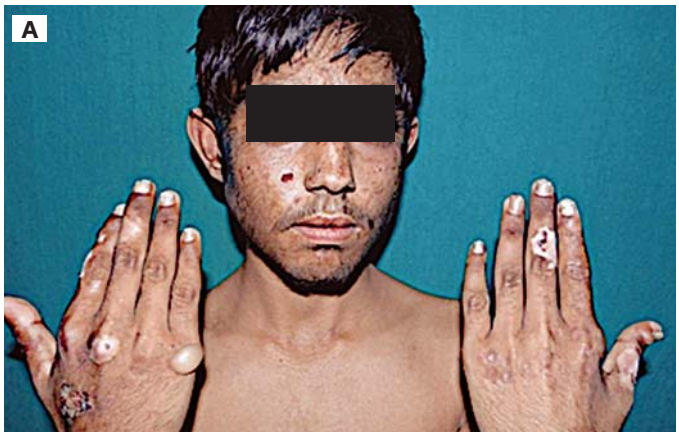
Pathogenesis

The pathophysiologic mechanism of pseudoporphyria is poorly understood. Pseudoporphyria in chronic renal failure may be precipitated by furosemide and other diuretics. Blisters are presumed to result from ultraviolet (UV)-induced free-radical injury to skin and blood vessels. Patients with chronic renal failure undergoing hemodialysis maybe more vulnerable to free-radical injury because of defective antioxidant mechanisms reflected by decreased levels of glutathione in plasma and circulating erythrocytes.

Clinical Features

Vesicles, bullae, skin fragility, milia, and scarring occur on sun-exposed skin. The dorsal hands are most commonly affected, but fingers, extensor legs, upper chest, or face may also show lesions (Figs. 28.5 A and B). In contrast to PCT, hypertrichosis, hyperpigmentation, sclerodermoid changes, and dystrophic calcification have been reported less frequently.

Additionally, in children, facial scarring resembling erythropoietic protoporphyria (EPP) may be found.



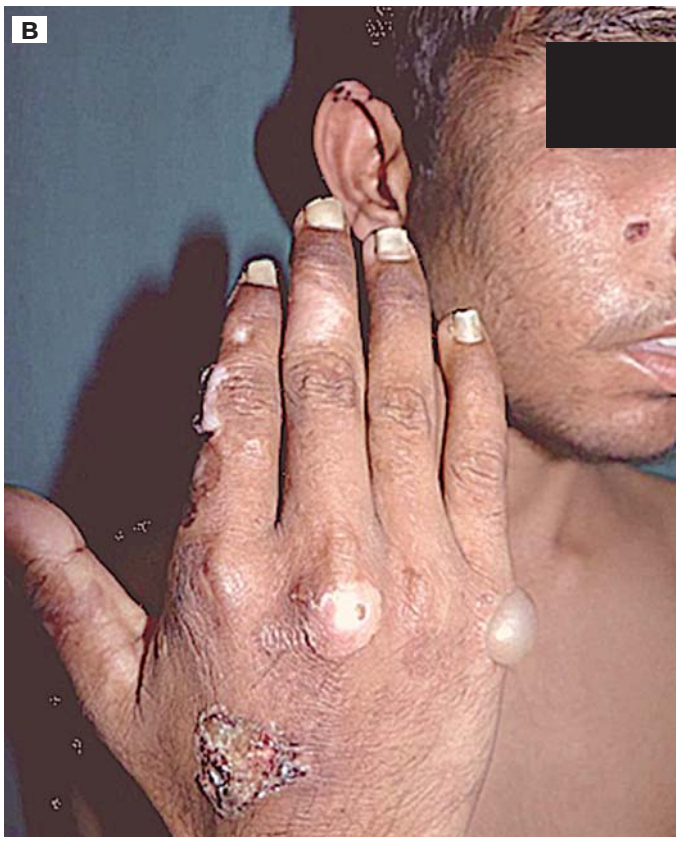


Fig 28.5: (A) Vesicles, pustules and scarring over face and dorsa of hands in pseudoporphyria due to naproxen; (B) A closer view of the same patient. Note the hypertrichosis on face and crusting and scarring on face and hands.

Pseudoporphyria in children has primarily been reported with naproxen. Burning with sun exposure, waxy thickening of the skin, increased free red blood cell protoporphyrins, and familial transmission have not been reported in children with pseudoporphyria.

Diagnosis

The histologic and immunofluorescence findings of pseudoporphyria are similar to that of PCT. Subepidermal blistering with scarce inflammation, periodic acid-Schiff (PAS)–positive eosinophilic deposits around blood vessels are seen.

Histology

Subepidermal bullae with or without festooning of dermal papillae, scant to mild lymphocytic perivascular infiltrate, PAS-positive thickening of blood vessel walls, and sclerosis of collagen are observed.[17]

Immunofluorescence

Positive direct immunofluorescence (DIF) is suggestive of pseudoporphyria.[17] Indirect immunofluorescence is negative. Granular deposits of IgG and C3 are most commonly present at the dermoepidermal junction and in the upper dermal vasculature. Also, IgM, IgA, and fibrinogen maybe present.

Ultrastructural studies have shown cleavage occurring just beneath the epidermal basal lamina in pseudoporphyria.
By definition, porphyrin assays of red blood cells, plasma, urine, and feces are normal in pseudoporphyria.

Treatment

Those patients who require nonsteroidal anti-inflammatory drugs (NSAIDs) and develop pseudoporphyria should be switched to agents that have a less photosensitizing profile, such as diclofenac, indomethacin, and sulindac. Pseudoporphyria has not yet been reported with use of the newer cyclooxygenase-2 inhibitors. Treatment entails discontinuation of suspected agents and sun protection, especially against ultraviolet A (UVA) wavelengths.

CUTANEOUS PSEUDOLYMPHOMAS

Introduction

Cutaneous pseudolymphoma (CPL) refers to a heterogenous group of benign reactive T- or B-cell lymphoproliferative processes with diverse causes that simulate cutaneous lymphomas clinically and/

or histologically.[18–20] Lymphomatoid drug eruptions may present with T- or B-cell patterns. Cutaneous T-cell pseudolymphomas in most cases are caused by systemic treatment with antiepileptic drugs such as phenytoin (Fig. 28.6) or carbamazepine. Cutaneous B-cell pseudolymphomas are somewhat less frequent. Recently, two cases of B-cell pseudolymphomas resulting from antigen injections for allergy hyposensitization have been reported.

Also termed as drug-induced cutaneous pseudolymphomas or drug-induced pseudolymphoma syndrome, can be broadly classified into (1) anticonvulsant-induced pseudolymphoma syndrome; (2) CPL induced by other drugs.

Anticonvulsant-induced pseudolymphoma syndrome: The anticonvulsants such as phenytoin, carbamazepine, mephenytoin, phenobarbital, butobarbital, primidone, methsuximide, etc. can cause this distinct presentation. Clinically, a triad of fever, lymphadenopathy, and erythematous eruption with hepatosplenomegaly and moderate liver dysfunction is present in most patients.

The syndrome occurs typically 2–8 weeks of drug ingestion, but it takes a time frame of 5 days to 5 years for the occurrence of this presentation after the phenytoin therapy. It usually presents as solitary lesion but widespread erythematous papules, nodules, and plaques are also seen.

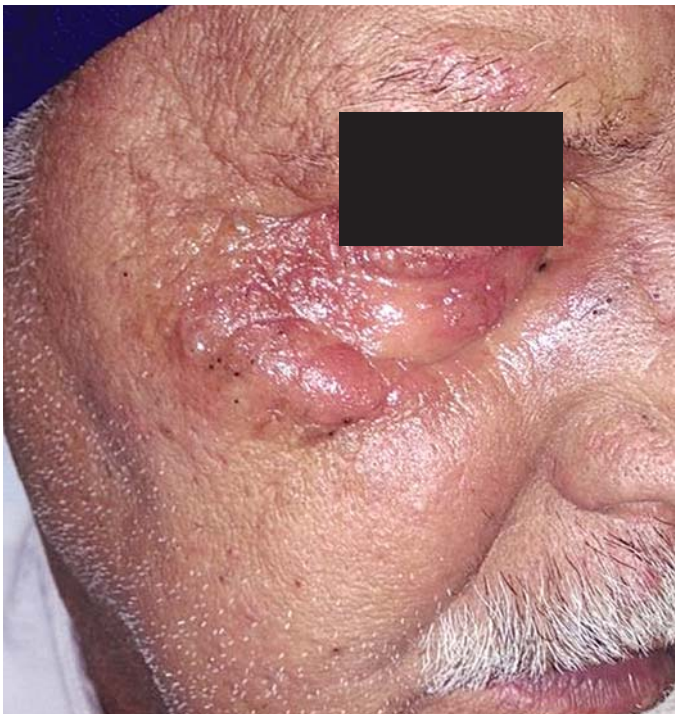


Fig. 28.6: Tumid, erythematous, indurated plaques of pseudolymphoma over infra orbital region in a patient on phenytoin for generalized seizures.

CPL induced by other drugs:[21-25] The duration of drug intake prior to eruption ranges from 1 to 11 months. Patients may have localized papules, nodules and plaques (Fig. 28.6), generalized papulonodular lesions, or even exfoliative erythroderma simulating Sezary syndrome. The drugs causing these eruptions are listed in Box 28.2.

Box 28.2: Drugs other than anticonvulsants causing CPL

Angiotensin-converting enzyme inhibitors, fluoxetine, clonazepam, rituximab, anti-TNF therapy (adalimumab, etanercept), atenolol, mexiletine, thioridazine, D-penicillamine, methotrexate, calcium channel blockers, tamoxifen, cyclosporine, zoledronic acid infusions, methylphenidate, and lornoxicam, vaccines (hepatitis A and B)

TNF - tumor necrosis factor.

Pathogenesis

1. Increase in absolute and relative number of peripheral T cells.
2. Drug-induced blastic transformation of lymphocytes.
3. Impaired ability of suppressor T-lymphocytes to suppress B-cell differentiation and immunoglobulin production.

Diagnosis

Clinical suspicion and withdrawal of drug is of utmost importance.

Histopathology

1. The anticonvulsant-induced pseudolymphoma syndrome shows focal necrosis, eosinophilic and histiocytic cell infiltrate, which destroys the normal lymph node architecture, as well as atypical lymphoid hyperplasia.
2. The CPL due to other drugs show either band-like infiltration of lymphocytes (MF-like) or nodular pattern simulation non-Hodgkin's lymphoma.

Treatment

Removal of offending drug leads to complete resolution within 1–8 weeks of stopping it. In anticonvulsant-induced CPL, if resolution does not occur, particularly in cases of phenytoin, search for overt lymphoma should be undertaken.

DRUG-INDUCED SCLERODERMA

Introduction

Drug-induced scleroderma has been rarely reported,

mostly with the features of diffuse scleroderma or acrosclerosis, and exceptionally with the characteristics of morphea.[26,27] Very recently, nephrogenic systemic fibrosis has been attributed to gadolinium-based radiocontrast media. Pseudoscleroderma lesions have been described in patients receiving various systemic drugs, such as bleomycin, peplomycin, L-tryptophan, carbidopa, gemcitabine, aldesleukin, taxanes, and balicatib.[28]

Texier's disease is a pseudosclerodermatous reaction that occurs after vitamin K injection , a subcutaneous sclerosis with or without fasciitis that lasts several years. Sclerodermoid injection site reactions have also been reported with pentazocine, progestin, tetanus toxoid, and vitamin B_{12}.

Etiology

Any drug can be safely ascribed to be inducing pseudoscleroderma or drug-induced scleroderma when–

1. There is temporal relation between drug administration and onset of sclerodermatous cutaneous manifestations.
2. No Raynaud's phenomenon, autoantibodies (antinuclear antibodies, anticentromere, antitopoisomerase, anticardiolipin, and antiphospholipid antibodies) undetectable and nailfold capillaroscopy is normal.
3. Improvement in the pseudosclerodermatous features after stopping the drug.

Skin thickening, telangiectasias, subcutaneous calcinosis, and scleroderma renal crisis occur with similar frequency in both forms of the disease (drug induced and classical), whereas Raynaud's phenomenon, arthritis, myopathy, esophageal disease, and pulmonary fibrosis appear to be more frequent in the classical form.

Pathogenesis

Immune modulating activities of chemotherapeutic drugs may be responsible, along with their direct chemical effect, for triggering the immune cascade that activates fibroblasts. Taxanes induce an increase in the serum levels of IL-2, IL-6, and GM-CSF. Adriamycin stimulates the production of IL-1, IL-2, and TNF from various cells in human and animal models.

Monocyte chemoattractant protein 1 and C-C chemokine receptor type 2 (CCR-2) signaling plays an important role in the pathogenesis of bleomycin-induced scleroderma.[29] Monocyte chemoattractant protein-1 may contribute to the induction of dermal sclerosis via its direct effect of upregulation of mRNA expression of extracellular matrix on fibroblasts, as well as indirect effect mediated by a number of cytokines released from immunocytes recruited into the lesional skin.

Histopathological Findings

An intact epidermis, perivascular inflammatory infiltrates (mainly composed of lymphocytes and plasma cells), and interstitial edema involving the dermis are seen. Fibrosis involves both the dermis and the hypodermis, and direct immunofluorescence is negative.

Treatment

Injection-induced scleroderma: High-potency topical steroids twice a day for up to 6 months; calcipotriene (Dovonex) have shown limited success in treating localized scleroderma. Calcipotriene works by regulating excessive collagen synthesis via inhibition of IL-2 secretion and T-cell modulation.

LEARNING ESSENTIALS

- Erythema nodosum is the most common presentation of drug-induced panniculitis.
- Drug-induced SS has a long list of causative agents with many immunomodulators and antineoplastic drugs being added to the list. Significantly elevated levels of helper T-cell type 1 cytokine level are also observed.
- DILE and DISCLE have increasingly been recognized as more and more cases and causative agents are being reported.
- Pseudoporphyria is a photosensitive blistering disorder with clinical and histological features identical to PCT, lacking serum and urine porphyrin abnormalities.
- CPL is a benign reactive T- or B-cell lymphoproliferative process with diverse causes that simulate cutaneous lymphomas clinically and/or histologically and are predominantly T-cell type.
- Drug-induced scleroderma is a rare disorder with many new drugs being increasingly recognized as a causative agent.

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Chapter

29

Anaphylaxis and Anaphylactoid Drug Reaction Patterns

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SUMMARY

Drug-induced anaphylaxis and anaphylactoid reactions are potentially life-threatening conditions requiring immediate multidisciplinary management. Penicillin is the most studied drug causing anaphylaxis. As newer drugs are marketed, occurrence of these reactions is on the rise. Currently, anesthetics, neuromuscular blockers, nonsteroidal anti-inflammatory drugs (NSAIDs), and newer antibiotics are the leading causes of anaphylaxis and anaphylactoid reactions. Anaphylaxis is due to IgE-mediated degranulation of mast cells and basophils; same mechanism is operative in anaphylactoid reactions, but without the involvement of IgE. Main presenting features include urticaria, angioedema, excess salivation and lacrimation, palpitation, vomiting and purging, restlessness, stridor, hypotensive shock, syncope, etc. Diagnosis is mostly based on history and clinical features. The available laboratory tests are not sensitive or specific. Adrenaline is the drug of choice. The patient must be managed in supine position with other life-support measures. Main causes of mortality are cardiovascular and respiratory compromise. Following an acute episode, patient must be observed in hospital so that late reaction is not missed. At the time of discharge, an information tag regarding the drug and outline of management must be provided to the patient. Detection of drug-induced mast cells and basophil-activation markers and estimation of drug-specific cytokines and chemokines shall bring a ray of hope in specific diagnosis of these reactions in future. In India, emergency physicians must be trained in the management of anaphylaxis.

INTRODUCTION

Anaphylaxis is an IgE-mediated immediate hypersensitivity reaction induced by various exogenous agents, presenting with abrupt onset, severe cutaneous, and systemic symptoms which may be potentially life-threatening and require immediate intervention.[1] The term "anaphylaxis" was coined by French physiologists Charles Richet and Paul Portier[2]. Discovery of this dramatic life-threatening condition succeeded Charles Richet to win Nobel Prize in 1913.[2]

Anaphylactoid reactions are symptom complexes similar to anaphylaxis but without the involvement of IgE in mast cell activation.

Anaphylaxis and anaphylactoid reactions can be mediated by various exogenous factors such as foods, drugs, venomous insect sting, and sometimes may be idiopathic. The discussion in this chapter will be restricted to drug-induced anaphylaxis and anaphylactoid reactions.

ANAPHYLAXIS

Epidemiology

Lifetime prevalence of anaphylaxis of any etiology is around 0.05–2%[1]; approximately 50% being triggered by food.[3] The incidence of drug-induced anaphylaxis is 1 in 5000 drug exposures (1 in 50,000–100,000 patients treated with penicillin may develop anaphylaxis).[4] Fatality has been recorded in <10% cases.[4] Penicillin is the most studied drug to understand anaphylaxis.[5] The rate of fatal anaphylaxis due to penicillin has been recorded to be 0.002%.[5] With widespread use of various newer drugs, the frequency of anaphylaxis is on the rise.[4,6]

Risk Factors

Various risk factors have been identified; although

drug-induced anaphylaxis may occur at any age, young and middle-aged populations are at higher risk. In childhood and adolescents (up to 15 years), boys are more commonly affected, whereas among adults, women are the frequent sufferers.[1,7,8] Drug administration at intermittent schedule and parenteral preparation pose higher risk than continuous dosage and oral regimen.[4] Atopic individuals and patients with cardiovascular and pulmonary morbidity may have exaggerated symptoms of anaphylaxis.[4,8] Anaphylaxis is most likely to occur in the community setting where health-care facility is not immediately available.[9]

Drugs Causing Anaphylaxis

Various drugs causing anaphylaxis have been presented in Box 29.1.[1,7,10–15] The most common drug causing anaphylaxis in the years 1960–1970 was penicillin. The current scenario is changing; drugs used in the perioperative period, like various anesthetics, neuromuscular blockers, other antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs) are taking the lead.[16]

Box 29.1: Drugs causing anaphylaxis[1,7,10–15]

- β-lactum antibiotics (penicillin, cephalosporins)*
- NSAID (aspirin, ibuprofen)*
- Ionic radiographic contrast media*[10]
- Preparations containing animal sera
- Vaccines containing egg albumin
- Chemotherapeutic drugs (platins and taxenes)[1]
- Local anesthetics (para-aminobenzoic acid component)*
- General anesthetics*
- Muscle relaxants (suxamethonium, pancuronium, vecuronium, atracurium, etc.) and recuronium*[11,12]
- H_2-receptor blocker (ranitidine)[13]
- Leukotriene-receptor antagonist (pranlukast)[14]
- Monoclonal antibodies; cetuximab, infliximab, omalizumab
- Oversulfated chondroitin sulfate (OSCS)-contaminated heparin*[1,15]
- Folic acid in vitamin and supplements
- Chinese herbal medications*[7]

* These drugs cause anaphylactoid reaction also

Pathogenesis

The drug allergen causing an episode of anaphylaxis is dose independent. In drug-induced anaphylaxis, the allergen may not be the medication itself, but its metabolites or intermediary breakdown products. Even other components of the drug preparation and preservatives may act as allergens. The classic example is adrenaline, the drug of choice in anaphylaxis. The metabisulfite content, used as preservative in adrenaline injection, may itself induce anaphylaxis.[17]

Anaphylaxis usually occurs during second exposure to a drug, but may also occur at the first encounter. The reason for the latter is prior exposure to the allergen from other sources, making the individual already sensitized. The metabisulfite content of adrenaline injections is used as preservative in many food and beverages, causing prior sensitization to it through food.[17] Similarly, women are more susceptible to develop anaphylaxis due to intravenous muscle relaxants during surgery. This is because of the quaternary ammonium ions in these preparations, to which the patient might have had prior sensitization through components of cosmetics.[5]

Mast cells and basophils are the main cells executing an episode of anaphylaxis. In addition to the drug allergen, there may be some non-immunologic trigger factors in the initiation of anaphylaxis. Physical exercise after intake of drug such as aspirin has been recorded as a trigger factor.[7] Other such trigger factors include exposure to cold breeze or water, and prior intake of drugs such as opioids and vancomycin.[1,18]

In response to the first exposure to the drug, susceptible individuals generate abundant IgE, which in turn enhances the expression of high-affinity FcεRI receptors on these cells (priming).[18]

On reexposure, drugs induce cross-linking of IgE and aggregation of high-affinity FcεRI receptors on these cells.[18] A series of intracellular events follow; there is activation of tyrosine kinase and influx of ionic calcium in mast cells.[18] This causes granular disruption and release of preformed mediators such as histamine, tryptase, carboxypeptidase, chymase, platelet- activating factor, proteoglycan, etc. These in turn lead to the activation of phospholipase A_2 and arachidonic acid pathway. There is liberation of prostaglandins and various leukotrienes. Other inflammatory mediators such as interleukin-6 and -33 (IL-6, IL-33) and tumor necrosis factor-α (TNF-α) also play a part.[18] There is endothelial barrier disruption (through endothelial Gq/G_{11}-mediated signaling) that promotes capillary leak in various organs and subsequently initiates organ-specific symptoms of anaphylaxis.[18]

Current opinion is that heart is a crucial target organ during an episode of anaphylaxis. This is because

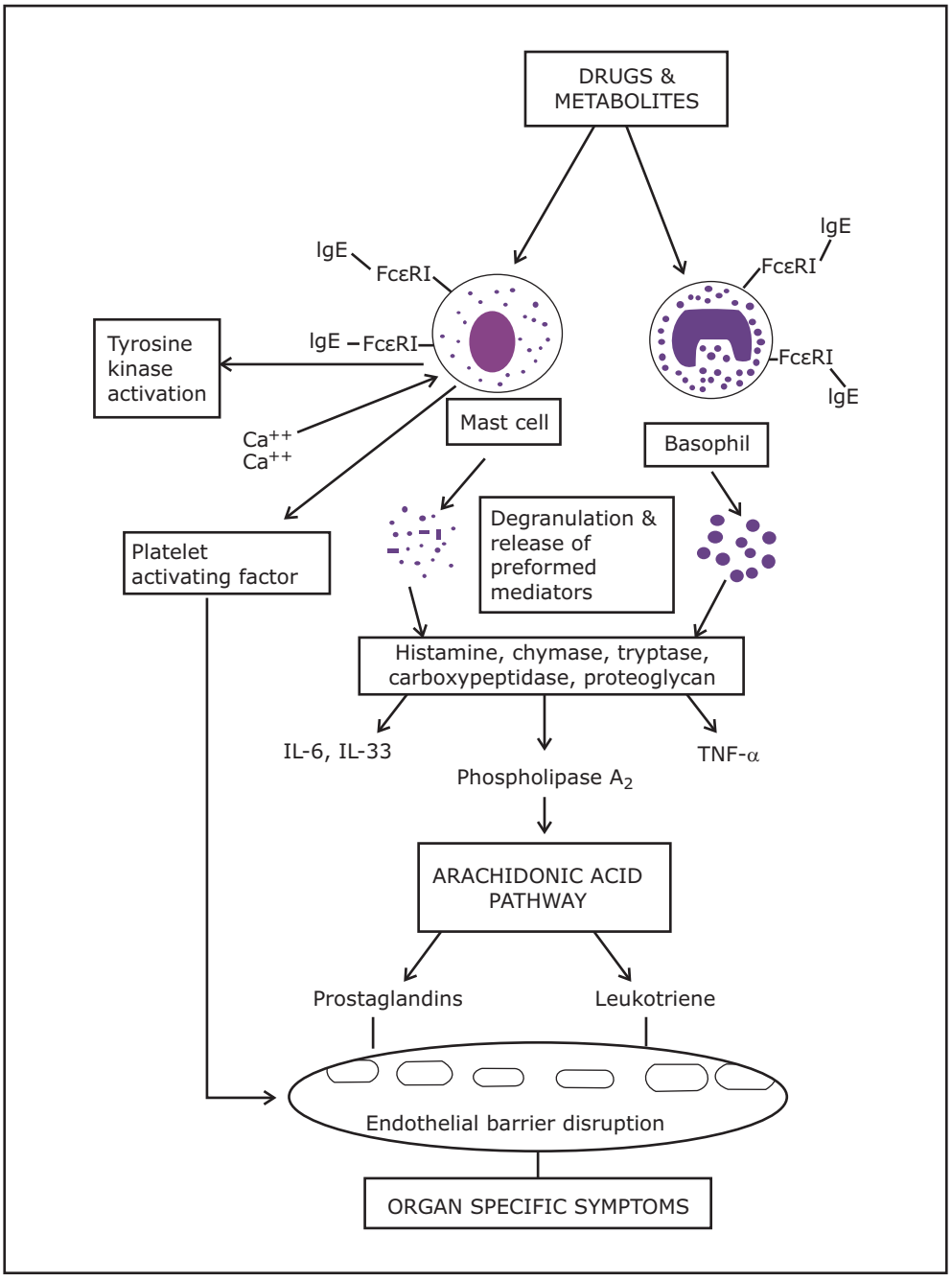

Fig. 29.1: Schematic representation of pathogenesis of anaphylaxis.

of predominance of mast cells in myocardium and intima of coronary arteries.[18] The histamine, prostaglandin D_2, and leukotriene C_4 liberated by myocardial mast cells induce coronary vasospasm.[18]

Figure 29.1 represents main steps in the pathogenesis of anaphylaxis.

Clinical Features

The onset of symptoms is sudden within minutes to hours (mostly within 1 hour) of the drug administration. Intense pruritus, urticaria, and angioedema are the initial features followed by flushing, headache, abdominal pain, vomiting, diarrhea, stridor, palpitation, hypotension, and shock. The patient is extremely restless and may describe it later as a sense of "impending death." Often a patient is brought in a "sinking-down" state with cold, clammy extremities because of hypotensive shock. Respiratory distress or frank stridor may be accompanied.

Skin is the most frequent organ of manifestation (80–90%).[1] The frequency of involvements of other organs are: respiratory tract (70%), gastrointestinal

tract (30–45%), cardiovascular system (10–45%), and central nervous system (10–15%).[1] These symptoms are present in varying combination and the intensity may be different. Hypotensive shock, so characteristic of the disorder may sometimes be absent and respiratory symptoms prevail. Various organ-specific clinical manifestations of anaphylaxis have been presented in Table 29.1.

Table 29.1: Organ-specific symptoms of anaphylaxis

Organ involved	Symptoms
Skin	• Flushing • Pruritus • Urticarial wheals • Angioedema
Mucous membrane	• Excess salivation • Itching and tingling of tongue and palate • Angioedema (swollen lips, tongue, uvula) • Conjunctival congestion and excess lacrimation
Gastrointestinal	• Abdominal cramp • Nausea and vomiting • Purging
Respiratory tract	• Sneezing and rhinorrhea • Constriction of chest • Hoarseness of voice (laryngeal edema) • Stridor (laryngospasm) • Wheeze and cough (bronchospasm)
Cardiovascular system	• Palpitation • Hypotension • Hypovolemic shock • Collapse • Arrhythmia • Myocardial infarction during the acute episode in already compromised heart (even in absence of adrenaline use)
Central nervous system	• Anxiety • Headache • Dizziness • Confusion • Tunnel vision[9] • Hypotonia • Incontinence • Syncope

In some patients, the episode is milder and these patients may appreciate premonitory symptoms such as dizziness, fainting attack, tingling sensation on skin and oral cavity, and redness of eyes. A biphasic course (late reaction) has been described in some patients (20%)[4]; there is recurrence of symptoms after a gap of about 1–8 hours (up to 72 hours) of resolution of the initial episode even in absence of further exposure to the inflicting drug.[4]

Course of the Disease

Onset, severity, and course of anaphylaxis are unpredictable. Sometimes it may be mild and resolves spontaneously.[1] A person having a mild episode earlier may develop a deadly episode on subsequent exposure.[9] Mostly it has a fatal course and unless rapid intervention is instituted, patient goes downhill due to hypotensive shock. Severity and fatality of anaphylaxis are directly related to the rapidity of its evolution.[4] Death may occur due to cardiovascular failure and/or respiratory obstruction.

Diagnosis

Diagnosis of drug-induced anaphylaxis is based on a thorough history taking and clinical features. Immediate onset of symptoms following drug administration should raise the suspicion. Every patient may not develop all features of anaphylaxis at one time and incomplete clinical presentation should not be a bar to suspect anaphylaxis. Diagnostic criteria for anaphylaxis have been formulated by a multidisciplinary group of experts during the first and second symposia on the definition and management of anaphylaxis (2005 and 2006); these are available in the cited references.[19,20] Following exposure to a drug (or other allergens), if any one of these three criteria is fulfilled, diagnosis of anaphylaxis is highly likely.[4,21,22] However, these diagnostic criteria are not specifically meant for drug-induced anaphylaxis.

Laboratory tests are not essential for the diagnosis of anaphylaxis. However, there are numerous biomarkers of mast cell and basophil activation. Some of these can be used for confirmation of an episode of anaphylaxis.[18] These include the following:

- **Plasma & Urine histamine level**: Plasma levels can be determined after 15 minutes to within 1 hour of onset of symptoms.[18] The blood should be drawn through wide-bore needles, kept in cold temperature, centrifuged immediately, and the plasma is kept frozen.[18] Urinary histamine and its metabolite, N-methylhistamine can be assessed in 24-hours urine sample.[18]
- **Plasma/serum total tryptase level**: It should be estimated between 15 minutes to 3 hours of the onset of symptoms.[18] This is helpful when anaphylaxis is preceded by injectable drug exposure (not administered by enteral route) and associated with hypotensive shock. Paired test is more meaningful at peak of the episode and after complete resolution of symptoms.[18]

A wide array of other biomarker assays are available, but estimation of all these including the above two have low sensitivity and specificity in the diagnosis of anaphylaxis.[18] Estimation of allergen-specific IgE level is not routinely performed for drug-induced anaphylaxis. Clinician-supervised skin test can ideally be performed 3–4 weeks after an episode to confirm the trigger drug.[18] This constitutes the gold standard in diagnosis of drug-induced anaphylaxis.[18] However, except for β-lactam antibiotics, drug allergens for skin test are not available commercially.[18]

Skin test (prick test or intradermal test) with major and minor determinants of penicillin help in identifying people at risk of anaphylaxis to this drug.[21] The major determinant (benzylpenicilloyl poly-L-lysyl/pre-Pen) and penicillin G are commercially available for this purpose and can detect 90%–97% susceptible cases.[21] However, full battery of reagents (both major and minor determinants) must always be used for these tests so that individuals sensitive to minor determinants are not missed.[21] Such tests should be conducted in hospital so that emergency management is easy to access in case anaphylaxis is induced.[21]

Differential Diagnosis

Many conditions may mimic some or individual symptoms of anaphylaxis and may be mistaken as anaphylaxis. Various differential diagnoses of anaphylaxis have been presented in Box 29.2.

Box 29.2: Differential diagnoses of anaphylaxis

- Anaphylactoid reaction
- Severe acute urticaria and angioedema
- Vasovagal attack
- Acute episode of asthma leading to respiratory decompensation
- Pulmonary embolism
- Shock of other etiology (hemorrhagic, cardiogenic, septicemic)
- Carcinoid syndrome
- Pheochromocytoma
- Any type of mastocytosis or clonal mast cell disorder
- Acute anxiety (panic attack)
- Foreign body aspiration (children)
- Consumption of certain dietary items (monosodium glutamate, sulfites used as food preservatives, scombroid fish poisoning)

Management

Anaphylaxis is an acute, life-threatening illness. If occurred at hospital, cardiopulmonary resuscitation remains at hand. In case it occurs at home, the patient must immediately be shifted to an intensive care unit in a well-equipped ambulance with oxygen cylinder, other life-saving instruments and trained health-care personnel. The clinical presentation and eventualities are stormy and gives little time to the clinician to take decision. Many of the failures in treating cases of anaphylaxis are due to delay in recognition of the condition and postponement in initiating specific therapy.

Supportive Management

Once hospitalized, following supportive measures must be instituted instantly:

- Supine position with elevation of lower limbs (except during vomiting).
- Maintenance of airways and oxygen inhalation.
- Intravenous line (with large-bore needle) with fluid rehydration, and urinary catheterization.
- Tracheostomy in presence of stridor.
- Calculation of body weight for further drug administration.

Specific Therapy

Adrenaline is the drug of choice for management of anaphylaxis as it is a physiological antagonist of histamine,[22] and there is no absolute contraindication for its use in this clinical condition.[22] Following steps are followed:[1,2,4,5,18,22]

- Immediate administration of injection adrenaline (1:1000) solution, (0.01 mg/kg) maximum 0.5–1 mL, intramuscular (IM) on mid-anterolateral aspect of thigh (because this provides larger surface area and ensures faster absorption). The dose may be repeated every 5–20 minutes, if necessary.
- Intravenous (IV) fluid (normal saline/5% dextrose solution/colloidal volume expanders), particularly in patients with persistent hypotension despite adrenaline dosage.
- If there is no relief of symptoms of anaphylaxis with the above treatment, adrenaline infusion may be started under supervision of an experienced physician conversant with continuous cardiovascular monitoring.
- If IM adrenaline and IV fluid replacement fail to correct hypotension, dopamine infusion (2–20 μg/kg/minute) may be started and adjusted according to individual patient's need.
- Patients on prior β-blocker therapy develop refractory hypotension and have high fluid requirement. These patients may be started

with IV glucagon (1–5 mg initially, followed by infusion at the rate of 5–15 µg/minute according to patient's response).[5]

Adrenaline has multipronged effect in anaphylaxis. It increases blood pressure by vasoconstriction and raise peripheral vascular resistance (α-1 receptor effect); exerts inotropic effect on myocardium and increases heart rate (β-1 receptor effect); decreases mucosal/laryngeal edema (α-1 receptor effect); enhances bronchodilation and decreases release of inflammatory mediators (β-2 receptor effect).[18]

In certain situations, adrenaline may appear ineffective in anaphylaxis. A delay in first dose, inadequate dose, subcutaneous administration, and patient kept in upright position (empty vena cava syndrome) are the main causes for non-responsiveness.[18]

- In presence of bronchospasm; injection aminophylline 250 mg IV is administered over 5 minutes; thereafter it is continued as 250 mg by slow IV infusion (over 6 hours) mixed in 500 mL normal saline. Otherwise, terbutaline/salbutamol nebulizer may be used.
- In presence of urticaria/angioedema/intense pruritus, injection chlorpheniramine maleate (10–20 mg) IV or injection hydroxyzine 25–50 mg administered IM. This can be repeated 6 hourly. A combination of H_1 and H_2 antihistamines may also be administered.
- Corticosteroids: Role of corticosteroid in the management of anaphylaxis is controversial as they have a slower onset of action. However, it may be helpful in protracted cases and in preventing the biphasic reaction. Following dose may be used:

Injection hydrocortisone (250 mg) administered IV immediately, thereafter 100 mg 6 hourly. Once the patient is stabilized, oral prednisolone should be started (40 mg/day for 3 days).

Medical Supervision

All patients with an episode of anaphylaxis must be kept under supervision of the medical team for a minimum period of 4–6 hours or more to avoid the risk of biphasic reaction.

Care of Comorbid Conditions and Concurrent Drugs

Patients with concurrent bronchial asthma, chronic obstructive pulmonary disease or any other chronic lung disease, hypertension, and ischemic heart disease should be kept under medical supervision for an extra period.[1,2,4,5] In all patients having an episode of anaphylaxis, possibility of underlying mast cell disorder must be ruled out.[18]

Patients who are on treatment with β-blockers, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), monoamine oxidase (MAO) inhibitors, and some tricyclic antidepressants need special caution.[1,2,4,5] β-blockers blunt the physiologic response of adrenaline during the therapy.[4] Moreover, these patients may develop profound hypotension, requiring massive intravenous fluid therapy.[4] ACEI and ARBs inhibit body's own compensatory mechanisms to tackle the hypotensive crisis.[4] MAO inhibitors and tricyclic antidepressants enhance the side effects of adrenaline, such as tachycardia and hypertension.[4] Intake of first generation H_1-antihistamines such as diphenhydramine, and chronic alcoholism deters recognition of symptoms of anaphylaxis.[18] All these drugs are associated with a poor outcome in anaphylaxis. Hence, eliciting history of concurrent illness and prior drug intake is very important in all patients in the recovery phase.

Instructions to a Patient of Anaphylaxis at the Time of Discharge

Any patient with an episode of anaphylaxis and their immediate caretakers must be counseled thoroughly for avoidance of the causative and related drugs. They must be provided with a "medical identification tag" (card, bracelet/necklace/badge) with various anaphylaxis-related information (Box 29.3).

Box 29.3: Information to be included in medical information tag

- Mention of the drug causing the last episode of anaphylaxis
- A list of cross-reacting drugs
- Immediate management protocol of anaphylaxis
- Address and contact details of the medical team who treated the patient during last episode
- Contact details of patient's immediate care-takers
- A list of "dos" and "don'ts" in anaphylaxis

Adrenaline auto-injectors (EpiPen®, Twinject®) are available for first aid use by the patient or family members in emergency situation. However, these are available in fixed dosage (0.15 and 0.3 mg) and are meant for subcutaneous administration.[18] Subcutaneous administration of adrenaline is not recommended in anaphylaxis and the fixed dosage may be inadequate for an average adult person.

Moreover, use of such device at home may give a false sense of security to the patient, actually delaying the specific management.[18]

All patients having an episode of anaphylaxis must be referred to an allergist/immunologist for detailed workup and further counseling regarding preventive measures.

Role of Drug Desensitization

Desensitization protocol for penicillin is available and the cited reference provides the details.[23] It can be used for conditions where penicillin is the only therapeutic option (neurosyphilis, congenital syphilis, and syphilis during pregnancy).[23] It is a simple procedure but should always be performed in hospital setup with due care. Either oral or intravenous route can be used for desensitization but the former is preferred. Small upgraded dosage of penicillin V suspension is administered at intervals of 15–30 minutes (total cumulative dose 1.3 million unit) over a period of 4–12 hours. Following this, the first oral dose of penicillin can be administered (observation period of 30 minutes if intravenous route is used).[23]

Future Directions

Development of rapid diagnostic tests with higher sensitivity and specificity which can be interpreted during an acute episode of anaphylaxis is the need of the hour. The currently available skin-provocation tests for some drugs are time-consuming and carry inherent risk of clinical reactivity.[18] Various *in vitro* tests are under research to overcome this hurdle; these include assessment of allergen-induced basophil-activation markers (CD63, CD203c), estimation of allergen-specific cytokines and chemokines, and use of dialyzed or recombinant antigens for skin tests.[2]

In India, "anaphylaxis education" must be made compulsory for emergency caregivers, including physicians and nurses. An adrenaline kit must be kept handy and a therapeutic protocol must be displayed in all emergency rooms so that undue delay in intervention can be avoided. A dedicated website for anaphylaxis management may be launched by the ministry of health care, which can be accessed by physicians and patients as well.

ANAPHYLACTOID REACTION

Various names are in use in the published literature to indicate drug-induced anaphylactoid reactions and this name is no longer favored.[1] These terminologies are "acute allergic reaction", "hypersensitivity reaction", "Kounis syndrome", non-IgE-mediated pseudoallergy, etc. Kounis syndrome is a distinct subset where there is acute vasospasm of epicardial coronary arteries (rarely, mesenteric and cerebral arteries) resulting from drug-induced mast cell activation.[24]

Almost all drugs causing anaphylaxis may also cause anaphylactoid reaction (marked with * in Box 29.1). In addition, there are anecdotal reports of several other drugs which have been reported to cause anaphylactoid reaction (Box 29.4).[24–29] Adrenaline injection, the drug of choice for anaphylaxis, may also cause severe anaphylactoid reaction due to its metabisulfite content, used as preservative.[16,24,30]

Box 29.4: Other drugs causing anaphylactoid reaction[24–29]

- Antibiotics (amoxicillin-clavulanic acid,[24] ciprofloxacin[25])
- Antineoplastic drugs (methotrexate,[26] amifostine[27])
- Dextran
- Corticosteroids
- Proton pump inhibitors[24]
- Anticoagulants[28]
- Intravenous vitamin K[29]
- Thrombolytics[25]
- rt-PA

Several pathways are involved in drug-induced anaphylactoid reaction, studied in animal and cellular models;[31] These include "direct stimulation pathway", "complement pathway", "coagulation pathway", " the kallikrein-kinin pathway", etc.[31] Some drugs (NSAIDs) may act as haptens to induce such reactions.[32] The mediators involved in anaphylactoid reaction remain almost similar to anaphylaxis, but here, their liberation from mast cells and basophils is not mediated by cross-linking of drug-specific IgE. Mast cells have the unique property of antibody-independent responsiveness to a myriad of cationic substances, including drugs, categorized as "basic secretagogues". Recent animal studies indicate that this basic secretagogues activate mast cells by binding to Mas-related G-protein–coupled receptor members (MrgprB2 and MrgprX2).[33]

Clinically, drug-induced anaphylactoid reactions are indistinguishable from anaphylaxis and the treatment does not differ. Similar to anaphylaxis, anaphylactoid reactions are also unpredictable, have varying severity, and often have a lethal outcome. During an acute episode, it is pointless to attempt differentiating the two conditions diagnosis and treatment wise.[1] However, once the patient settles down, it is imperative to review the case to understand the underlying pathomechanism involved, so that future risk reduction strategies can be undertaken.[1]

LEARNING ESSENTIALS

- Drug-induced anaphylaxis is a severe hypersensitivity reaction resulting from IgE-mediated release of mediators from mast cells and basophils.
- Drug-induced anaphylactoid reactions are similar to anaphylaxis symptomatology and management wise; but the pathomechanism is non-IgE mediated.
- Drug-induced anaphylaxis and anaphylactoid reactions are life-threatening and every second counts in the management.
- Patient must be in supine position with life-support measures.
- Adrenaline is the drug of choice.
- Intramuscular adrenaline dose, administered on mid-anterolateral thigh is recommended.
- After an acute episode, patients must be under supervision, so that biphasic reaction is not missed.
- Hypotensive shock is the leading cause of mortality followed by laryngeal or bronchospasm.
- Comorbid illnesses and concomitant therapies must be taken care of.
- On discharge, all patients must be equipped with an anaphylaxis information sheet.

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Chapter

30

Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

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SUMMARY

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe, life-threatening mucocutaneous adverse drug reactions with a high morbidity and mortality that require immediate medical care. The various immunomodulatory treatments for this condition include systemic corticosteroid, cyclosporin, intravenous immunoglobulin, cyclophosphamide, plasmapheresis, and tumor necrosis factor-α inhibitors. The ideal therapy still remains questionable as there are only a limited number of studies of good quality comparing the usefulness of different specific treatments.

INTRODUCTION

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), the latter also known as Lyell's syndrome, are terms used to describe a spectrum of delayed-type hypersensitivity phenotype involving at least two mucosal surfaces, usually triggered by drug, but can also less commonly occur secondary to infection. SJS is used to describe the less severe spectrum in which there is <10% body surface area (BSA) detachment; TEN for cases with >30% BSA detachment; and SJS/TEN overlap for those with 10%–30% BSA detachment.[1] The mortality for SJS is <10%, with the figure rising to 30% for TEN; overall SJS/TEN mortality is about 22%.[2] SJS occurs in up to seven cases per million population per year. TEN occurs in about two cases per million per year. Drugs are implicated in approximately 70% cases of SJS and almost all cases of TEN. About 200 drugs are implicated in this condition[3] and the number is on the increase.

RISK FACTORS

Drugs associated with the highest relative risks in this group of conditions include sulfamethoxazole (in combination with trimethoprim), carbamazepine, phenytoin, phenobarbital, nonsteroidal anti-inflammatory drug of the oxicam type, allopurinol, chlormezanone, aminopenicillins, cephalosporins, quinolones, and cycline antibiotics, along with nevirapine and lamotrigine (last two being dose related).

Drugs with low incidence of SJS/TEN include digoxin, acetaminophen, aluminum hydroxide, ascorbic acid, castor oil, chloral hydrate, codeine, corticosteroids, erythromycin, multivitamins, potassium chloride, promethazine, spironolactone, nitroglycerine, and aminophylline.

There are several single-case reports of newer drugs, such as on afatinib, a tyrosine kinase inhibitor, associated SJS.[4]

Other risk factors for SJS/TEN include the following:

- Human immunodeficiency virus (HIV)
- Radiotherapy
- Lupus erythematosus
- Bone marrow transplant and graft-versus-host disease
- Herpes simplex, mycoplasma
- Renal insufficiency

Factors that may be associated with drug-related cases include anemia and raised C-reactive protein >5 mg/dL.[5]

PATHOGENESIS

The sloughing and mucositis of TEN result from extensive keratinocyte apoptosis. The dermoepidermal junction involvement is mediated, at least in part, by the interaction of the Fas receptor and Fas ligand

[intravenous immunoglobulin (IVIG) works at this level by preventing this interaction, as well as by the protective effect of immunoglobulin G (IgG)]. It is a major histocompatibility complex (MHC) Class I–restricted reaction and HLA-B12 is involved in its occurrence.[6,7]

HLA-B* 1502 gene in the Han Chinese and Thai may predispose them to carbamazepine/oxcarbazepine-induced SJS/TEN. It has been calculated that 407 screenings are needed to prevent one case of TEN to this drug among Chinese.[8] It has also been seen that HLA-B* 5801 is associated with allopurinol-induced severe adverse drug reactions. Drug-specific T cell release of perforin granzyme–mediated cytotoxicity has been associated with TEN.[9] A recent article has shown that HLA-B* 59:01 in Japanese, Koreans, and Han Chinese predisposes them to methazolamide-induced SJS/TEN.[10] Also, HLA-A* 02:06 in Japanese and Koreans and HLA-B* 44:3 in Japanese, Indians, and Brazilians predispose them to cold medicine–induced SJS/TEN with severe ocular surface complications.[11]

The pathways involve cytotoxic CD8+ T cells. Granulysin, a cationic cytolytic protein that can kill a variety of microbes and tumor cells as well as serve as a chemoattractant with proinflammatory properties, can induce cell death via apoptosis in epidermal keratinocytes. Granulysin is found in particularly high concentrations, and the levels found in blister fluid correlate with the severity of the skin reaction.[12] Another possible pathway, involving the tumor necrosis factor-α (TNF-α) receptor-1 death pathway has been suggested and it is postulated that infliximab works in cases of TEN by acting on this pathway.[13] Patients with TEN have circulating autoantibodies to periplakin, supporting a humoral role as well in its etiology.[14] Endocan, a marker of endothelial dysfunction, is strongly associated with disease severity.[15]

In summary, the present thinking on the etiology of TEN involves cytotoxic T cells, which are activated by an inciting drug, which leads to the release of granzyme B and perforin, thereby activating the caspase cascade that ultimately results in keratinocyte apoptosis. Fas-Fas ligand binding activates caspase 8, which results in nuclease activation and the widespread skin blistering (Fig. 30.1).[16,17]

Hence, with these varying hypotheses, it may be possible that SJS/TEN might be a single clinical manifestation of multiple underlying, distinct pathophysiologies. It is possible that different treatment modalities for SJS/TEN might be effective at different stages of the disease or in different patient populations.

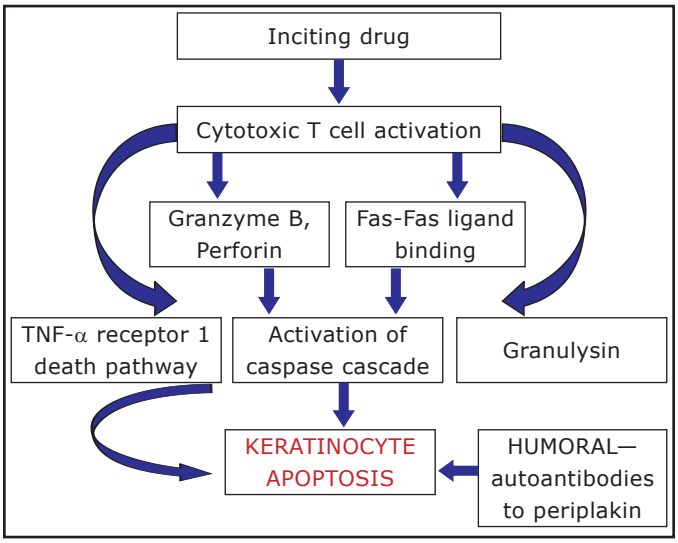

Fig. 30.1: Pathomechanism of TEN.

CLINICAL FEATURES

Most investigators believe that SJS and TEN are on a spectrum of severity and are different from the erythema multiforme group of diseases. In general, a prodrome of fever, malaise, and upper respiratory tract infection precedes the eruption by several days. Ocular inflammation may also develop before the skin signs. Cutaneous pain is a prominent early feature in SJS/TEN.

Early lesions are atypical targets that is different from the classic, raised, three-ringed iris lesions in cases of erythema multiforme to a more purpuric or erythematous two-ringed lesions. Initial sites of involvement are commonly the upper torso, proximal limbs, and face. Thereafter, lesions spread to involve the rest of the trunk and distal limbs. Lesional skin is tender to touch; minimal shearing forces will cause the epidermis to peel back. This fragility is demonstrated by so called Pseudo Nikolsky sign, which is not specific for SJS/TEN but is a helpful clinical indicator of epidermal necrolysis. Blistering ensues which progresses to extensive necrolysis resulting in the detachment of sheets of epidermis, leaving areas of exposed dermis that are prone to secondary infection. The typical clinical features are photographically delineated as under (Figs. 30.2 through 30.8).

Involvement of the mucous membranes of the eyes, mouth, nose, and genitalia is usually an early feature and leads to an erosive and hemorrhagic mucositis. Other organ involvement such as respiratory, GIT/hepatic/ENT/gynecological/genitourinary, and renal complications are also seen in a few patients.[18] Table 30.1 shows some complications seen in SJS/TEN.

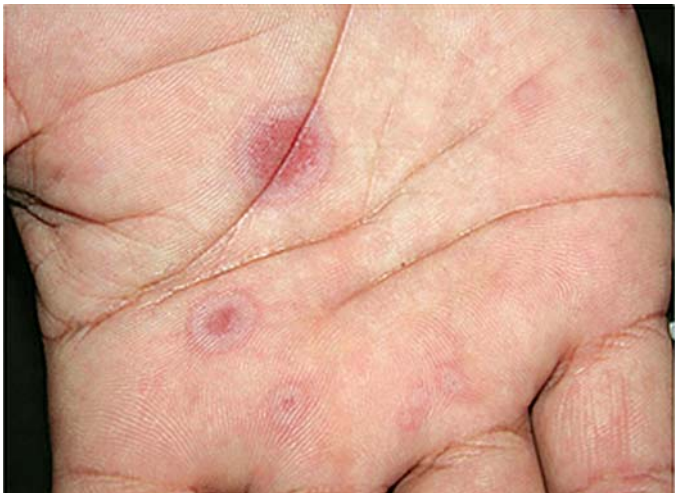

Fig. 30.2: Two ringed target lesion in a patient with SJS.

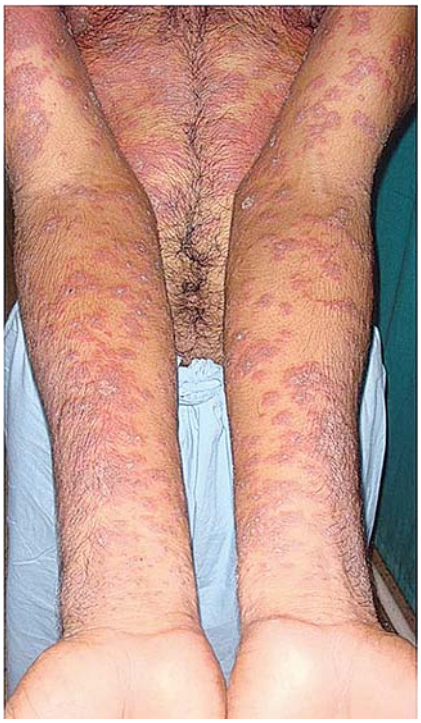

Fig. 30.3: Multiple target lesions with central scaling, crusting and purpura in SJS suspected to be due to carbamazepine.

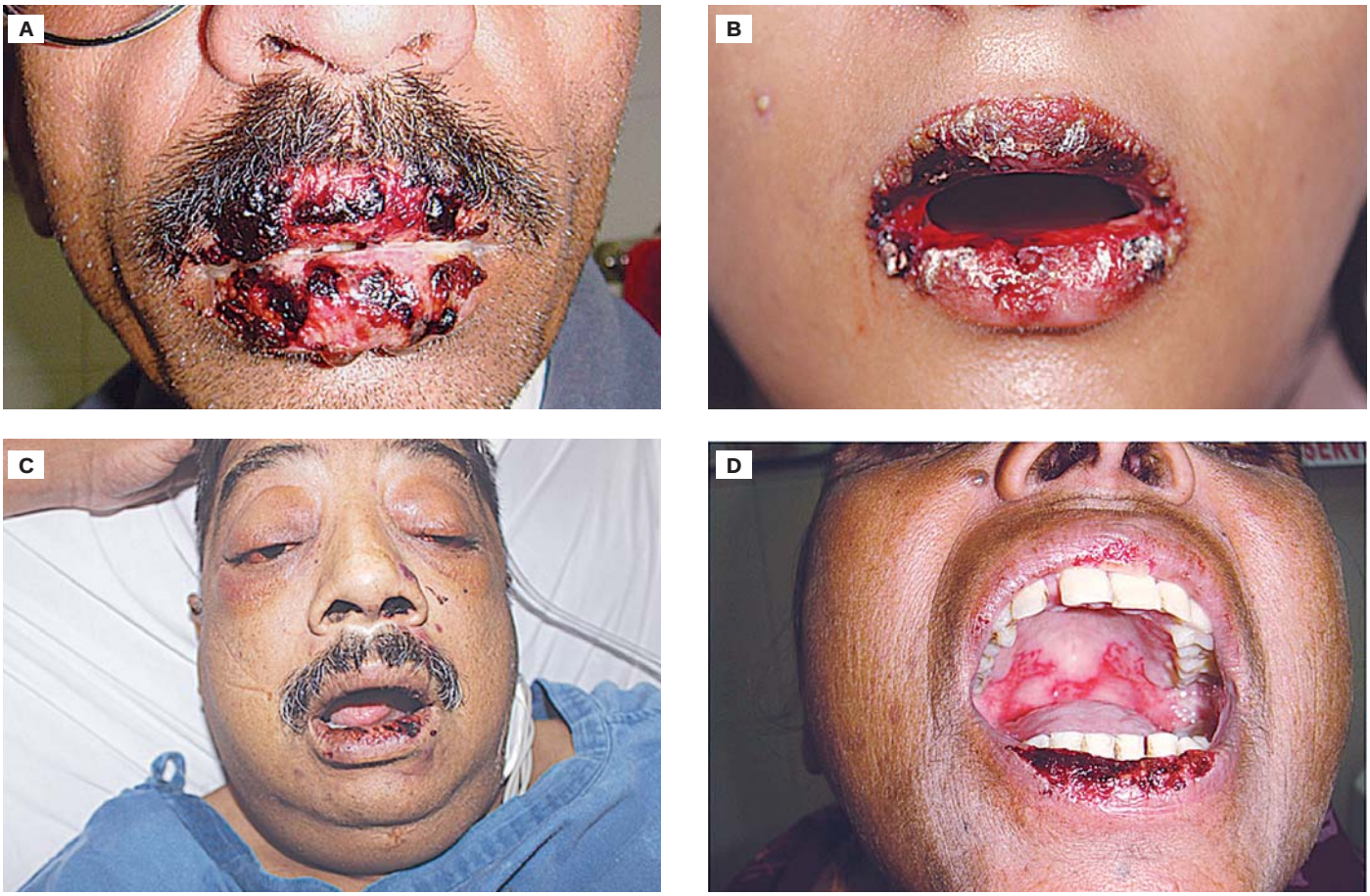

Fig. 30.4: (A) Characteristic hemorrhagic crusting of lips in SJS due to carbamazepine; (B) Hemorrhagic crusting and scaling of lips in a child with SJS on cotrimoxazole; (C) Conjunctival and oral mucosal involvement in SJS; (D) Hemorrhagic crusting on lips with oral erosions, in SJS patient.

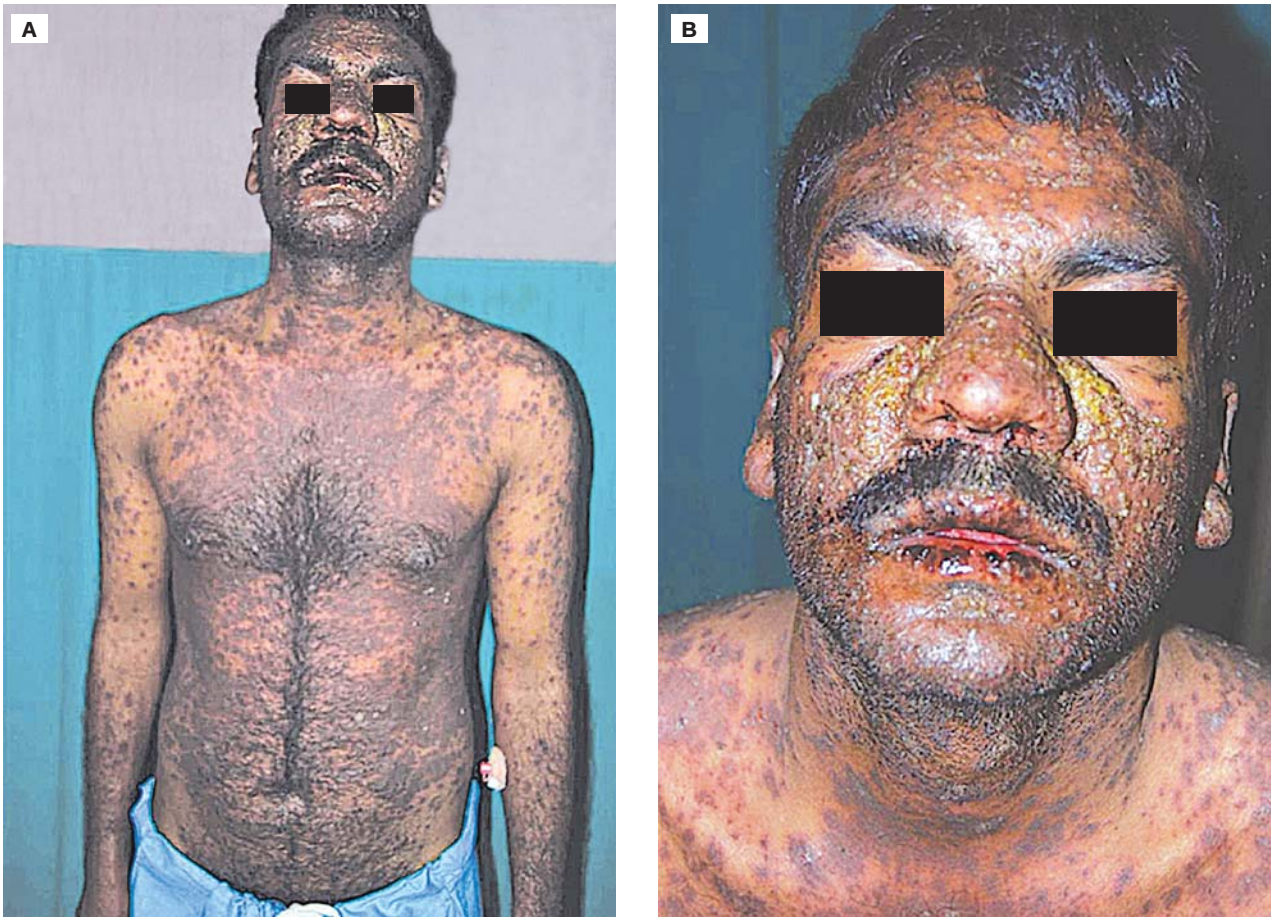

Fig. 30.5: (A) Extensive skin, lip and eye involvement of SJS-TEN in a patient on phenobarbitone; (B) A close up view of same patient with extensive skin and mucosal involvement.

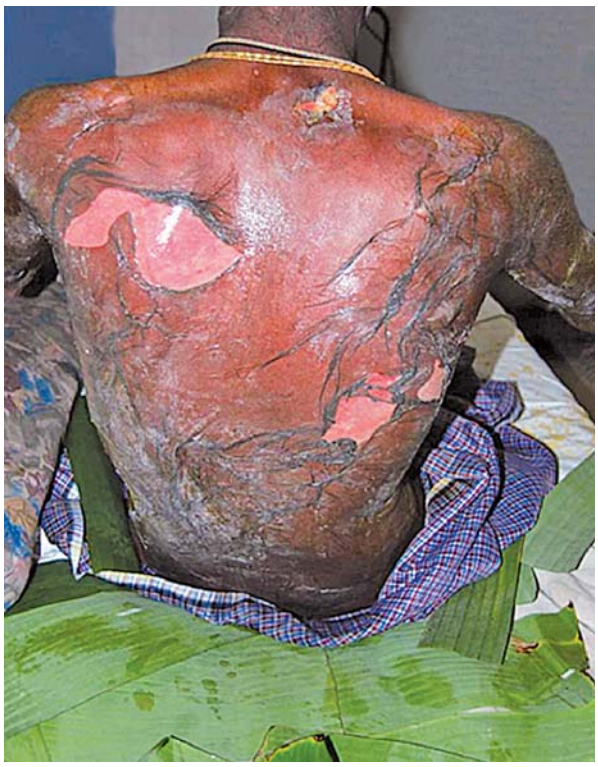

Fig. 30.6: Sheets of skin loss in TEN with banana leaf used for skin care.

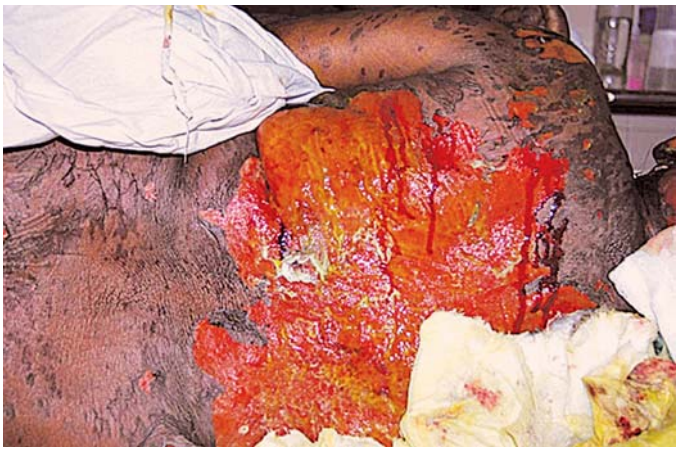

Fig. 30.7: Malignancy associated TEN in a lady with Stage IV carcinoma cervix.

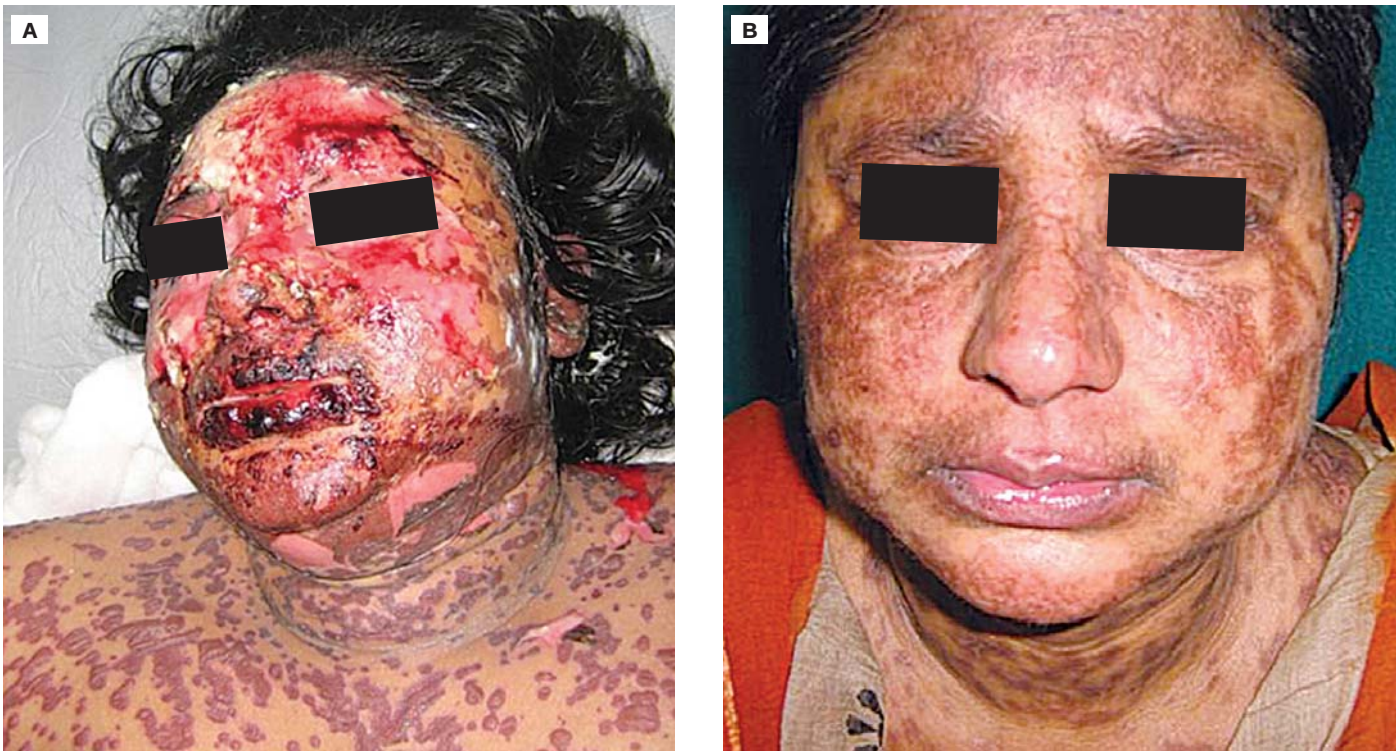

Fig. 30.8: (A) TEN patient before cyclosporin therapy; (B) TEN patient after cyclosporin therapy.

Table 30.1: Complications of SJS/TEN[19]

Cutaneous	Pigmentation abnormalities, nail deformities, alopecia
Ocular	Chronic conjunctivitis, pseudomembrane formation, trichiasis, corneal damage, cataracts, blindness
Respiratory	Bronchiolitis obliterans, bronchiectasis, chronic bronchitis
Gastrointestinal/ hepatic	Esophageal stricture, intestinal ulcer, chronic cholestasis, ischemic hepatitis, vanishing bile duct syndrome
Oral	Dental hypoplasia
Gynecologic	Vulval and vaginal adenosis, fusion of labia minora and majora, labial synechiae
Otolaryngologic	Hypopharyngeal stenosis, nasal septal synechiae, pinna synechiae
Renal	Glomerulonephritis
Hematological	Idiopathic thrombocytopenic purpura

Differential Diagnosis of SJS/TEN[20]

The diagnosis is usually easy to a trained dermatologist but sometimes the condition needs to be differentiated from the under mentioned conditions (Table 30.2).

HISTOPATHOLOGY

SJS/TEN are characterized by necrotic keratinocytes that are either disseminated or present in the form of complete epidermal necrosis. The basement membrane zone shows vacuolization resulting in subepidermal blistering. The dermis usually exhibits a scarce superficial and often perivascular lymphohistiocytic infiltrate.[21]

MANAGEMENT

From a practical standpoint, both SJS and TEN behave similarly and both carry significant morbidity and mortality.[22]

If SJS/TEN is suspected, discontinue any potential culprit drug immediately. The patient should undergo an evaluation of the critical disease components. Clinical examination includes an appraisal generic to any acutely ill patient, as well as assessments specific to SJS/TEN.

The SCORTEN (Table 30.3) is calculated within 24–48 hours of admission (the moment the initial laboratory

Table 30.2: Differential diagnosis of SJS/TEN

Erythema multiforme major	Acrally distributed, raised typical or atypical target lesions, more commonly caused by infections, particularly herpes and mycoplasma. Mucosal affection is generally milder with <2 sites involved. Systemic features, generally marked in SJS/TEN, are milder or absent. Recurrences are more frequent.
Pemphigus vulgaris	Affects middle-aged patients with flaccid blisters, erosions in scalp, trunk, flexures, and mucosal erosions.
Mucous membrane pemphigoid	Chronic, progressive disease, affects elderly patients with painful oral erosions, ulcers healing with scar, other mucosal involvement. DIF shows linear deposits of IgG, C3, and IgA.
Bullous pemphigoid	Affects elderly patients with prodrome of urticarial lesions and development of tense blisters. Mucosal involvement is rare.
Paraneoplastic pemphigus	Presence of pleomorphic eruptions with flaccid blisters, erosions, EM-like lesions with severe mucosal involvement in patients with underlying malignancy.
Bullous lupus erythematosus	May closely mimic SJS/TEN but histology and DIF are characteristic.
Linear IgA bullous dermatosis	May occur due to vancomycin. Annular configuration of bullae, rarity of mucosal involvement, and DIF showing linear deposits of IgA along the basement membrane.
Generalized bullous fixed drug eruption	Presence of well-demarcated round-to-oval erythematous dusky patches or plaques that may develop bullae in the center.
Bullous acute graft-versus-host disease	Seen in bone marrow and allogeneic hematopoietic stem cell transplant patients. Has a close clinical and histological resemblance to SJS/TEN but features such as acral to proximal spread, folliculocentric distribution, voluminous diarrhea, and jaundice are useful for differentiation.
Staphylococcal scalded skin syndrome	Affects infants and children, spares mucosa, and has superficial epidermal peeling.
Acute generalized exanthematous pustulosis	Commonly due to aminopenicillins; typically presents with sterile pustules on an erythematous background and lacks erosive mucosal lesions.

DIF - direct immunofluorescence; SJS - Stevens–Johnson syndrome; TEN - toxic epidermal necrolysis; EM - erythema multiforme.

Table 30.3: SCORTEN Predicted Mortality

Number of parameters	Predicted mortality (%)
0	1
1	4
2	12
3	32
4	62
5	85
6	95
7	99

investigations are available) and is calculated on the basis of the following seven parameters, each being given a score of 1:

1. Age above 40 years
2. Presence of malignancy
3. Tachycardia (heart rate above 120 beats per minute)
4. Initial percentage of epidermal detachment above 10%
5. Blood urea nitrogen above 28 mg/dL
6. Serum glucose above 252 mg/dL
7. Bicarbonate level less than 20 mmol/L

SCORTEN was initially meant to be a prognostic marker in cases of TEN. However, with improvements in the management outcomes of TEN due to various reasons, especially better supportive care, it has lost part of its significance as mortality rates are much lower than that predicted by SCORTEN. However, it is still a good indicator of the efficacy of a new modality of therapy.

Among the various factors, age of patient more than 70 years and BSA involvement more than 20% are associated with increased mortality.[23]

An algorithm, termed ALDEN (algorithm of drug causality in epidermal necrolysis), has been developed to help define drug causality in SJS/TEN. ALDEN is generally used as a tool for retrospective assessment of drug causality, and not for use in the acute phase of illness. However, the key parameters described in ALDEN can be applied as a useful framework for determining drug culpability in clinical practice.[24] It assigns each drug a score from −12 to +10 based on six parameters: (1) the time delay from initial drug intake to onset of reaction; (2) the probability of drug presence in the body on the index day; (3) a history of adverse reaction to the same drug; (4) the presence of

the drug beyond the progression phase of the disease; (5) the drug notoriety based on the previous results of the EuroSCAR study; and (6) the presence or absence of other etiologic causes. The score is categorized as very probable (>6), probable (4–5), possible (2–3), unlikely (0–1), and very unlikely (0).

APPROACH TO MANAGEMENT

The Cochrane summary on interventions in TEN eschews the use of thalidomide but recommends nothing. Hence, not a lot of Class I evidence exists for the therapeutic options that are mentioned from here on.

A multifaceted approach to the management of patients with SJS/TEN is required:

- Elimination of residual drug
- Immunosuppression
- Inhibition of Fas pathways
- General antiapoptotic strategies
- Aggressive supportive care

Therapy Points

- If Fas ligand and receptor binding has occurred prior to giving IVIG, downstream signaling continues unperturbed and programmed cell death follows.
- Hence, the importance of rapid disease recognition and treatment within 48–72 hours from the appearance of muco-cutaneous lesions.
- Therapeutic agent can be used as prophylaxis in those situations where a high risk of SJS exists.[25]
- Sucrose-depleted or nonsucrose IVIG is used to minimize the risks of renal failure; mortality is reduced compared to those receiving routine IVIG, corticosteroids, or only supportive therapy.[26] Volume also provides resuscitation. (However, the use of IVIG in all circumstances may not be relevant in all situations in our country; see later.) In children, there is evidence to suggest that steroids and IVIG improve outcome compared to supportive therapy alone.[27]
- Use of IVIG in patients with immunoglobulin A (IgA) deficiency is contraindicated because of increased risks of anaphylaxis (this can be found out by obtaining a thorough history, specifically querying the patient with regard to problems with recurrent sinopulmonary and gastrointestinal infections).[28]
- Corticosteroid-induced downregulation of nuclear factor-kappa beta (NF-κβ) in the presence of elevated TNF-α levels may be pro-apoptotic, and hence, needs to be guarded against.
- Silver nitrate maintains a moist wound environment, speeds re-epithelialization, minimizes pain, and decreases infection rates. Hypothermia and hyponatremia are risks associated with the use of these dressings to large BSAs.
- Avoid the use of sulfa-containing products because of the risk of systemic sensitization and leukopenia.
- Attention must also be paid to the mucous membranes and the pain associated with the mucositis seen in TEN and SJS.
- White petrolatum acts as an appropriate occlusive dressing to speed healing and minimizes the pain of cheilitis.
- Chlorhexidine rinses help minimize colonization of the damaged mucous membranes and maintain good oral hygiene.
- Use of skin substitutes and wound debridement varies among burn centers.

The following steps of the guidelines of the University of Florida, suitably modified with the IADVL guidelines, are helpful as a quick checklist[29,30]:

- Admit patient directly to the burn intensive care unit (BICU) or an intensive care setting.
- Discontinue unnecessary and suspected medications.
- Place large-bore intravenous lines or a central venous line in an area of uninvolved skin to ensure adequate intravenous access. If skin is involved proximally, the access should be distal to involved area.
- Obtain baseline laboratory tests, such as complete blood count, liver function tests, urinalysis, serum electrolytes, metabolic panel (including sugar, renal function parameters), chest X-ray films, other appropriate imaging or serologic tests including HIV, and an immediate (stat) IgA serum level if deficiency is suspected.
- Obtain punch biopsies of skin for diagnosis confirmation. An alternative for rapid diagnosis is removal of a bulla roof for immediate frozen sections to differentiate between TEN and staphylococcal scalded skin syndrome (SSSS).
- Culture skin, blood, body orifices (as appropriate), and urine daily to monitor for early infection, and keep abreast of changing antibiotic sensitivities. If barrier nursing is available, blood cultures are done at admission and then every 48 hours. If possible, culture of the skin and catheter tip every 48 hours is also suggested.

- Intake output charting.
- Barrier nursing and sterile handling of the patient along with regular hand hygiene with chlorhexidine hand rubs and hand washes as practiced by health-care workers and caregivers will help to prevent nosocomial infection.
- Look carefully for evidence of infection.
- Complications such as septicemia and disseminated intravascular coagulation can be monitored by specialized tests such as coagulation assays, D-dimer assay, and fibrin degradation products, where facilities are available.
- Use systemic antibiotics only for documented infections or signs of sepsis.
- Monitor fluid and electrolytes closely and begin total parenteral nutrition (TPN) in patients unable to take nourishment. Fluid requirement is usually two-third of that calculated by the Parkland's formula for burns, since the vascular structures are not involved in TEN (4 mL/kg body weight × percentage of BSA involved determined by the rule of nine with Ringer's Lactate) with fluid resuscitation in adults being commenced at 15% BSA involvement.[31] Half of requirement is administered in the first 8 hours and the remaining in the next 16 hours. After the first 24 hours, dextrose normal saline or normal saline may be used depending on the clinical situation.

A study by Shiga and Cartotto of 21 patients with TEN with extensive epidermal loss recorded fluid requirements over the first 3 days of admission and estimated that replacement volumes can be determined by the following formula: 2 mL/kg body weight/% BSA epidermal detachment.[32]

- Urine output should be maintained at 1000–1500 mL/day and the total fluid requirement (oral plus IV) should be urine output plus 500 mL.
- Caloric requirements are calculated as 30–35 kcal/kg/day. Proteins are given at approximately 1.5 g/kg/day, preferably by oral/nasogastric tube.
- Debridement of necrotic and desquamating areas may be performed.
- Consult ophthalmologist to assess ocular involvement.
- Consult otorhinolaryngologist to evaluate extent of upper respiratory tract involvement.
- Further consultations are driven by patient condition (i.e. internal medicine to manage comorbidities, pulmonary medicine for airway involvement, gastroenterology for alimentary involvement, and gynecology or urology for genitourinary involvement).
- Physical therapy daily to preserve limb mobility.
- Pain relief measures, such as patient-controlled analgesia (PCA) pump.
- Hydrotherapy (whirlpool) if needed.
- Detachable or detached skin should be used as a biologic dressing as far as possible. Nonstick dressings saturated with 0.5% silver nitrate every 3–8 hours if available can be used over denuded areas. Pre-impregnated dressings with silver nitrate are an alternative. The nanocrystalline silver dressings have shown considerable advantage over previously used dressings, with no adverse reactions noted and good healing of the skin lesions for all patients. Condy's compresses (potassium permanganate 1:10, 000) or petrolatum-impregnated gauze pieces are useful; Bactigras or collagen dressings may be used. Debridement is advised only for sloughed skin or necrotic skin that can no longer serve as a barrier.
- Avoid sulfa-containing topical or systemic preparations.
- Oral care with chlorhexidine rinses and white petrolatum to lips.
- Air-fluidized or water bed may be used to minimize shearing force.
- Keep room warm to prevent hypothermia (a temperature of 30–32°C should be maintained). Studies in burns patients have demonstrated that, at room temperature (24°C), energy expenditure increases by 40% of basal metabolic rate (BMR) with skin loss of 10% BSA, whereas at 80% BSA skin loss, energy expenditure increases by 120% of BMR.[33,34] The same thermoregulatory dysfunction occurs in extensive epidermal necrolysis and therefore a raised ambient temperature is necessary in SJS/TEN patient care to reduce energy consumption and associated metabolic stresses.
- Foley's catheter and nasogastric tube placement only when necessary.
- Avoid unnecessary manipulation of skin. Adhesive tape should not be applied directly to involved skin when possible.
- Baby shampoo for cleansing hairy areas daily.
- Mineral oil or petrolatum for dry skin.
- Skin substitute grafting (porcine xenografts or artificial skin) based on BICU protocol.

Use of IVIG (Level of Evidence II, Strength of Recommendation B)

Earlier enthusiasm for IVIG has been tempered by other studies showing that it did not significantly benefit patients with TEN and may even be harmful, especially in patients with renal impairment. There was risk of thromboembolism, hemolysis, vasomotor symptoms, anaphylactic reactions, and acute renal failure.[35,36] In another study, no benefit was found in mortality or progression of SJS and TEN.[37] In another review with SCORTEN analysis, 27% mortality with IVIG with 30% predicted mortality was seen, and hence, there was no dramatic benefit.[38] In another study conducted in Singapore, it was seen that high-dose corticosteroids were effective in SJS, whereas IVIG were useful in TEN and SJS/TEN overlap syndrome, hence eschewing its benefit in the entire spectrum of this disorder.[39] IVIG, preferably sucrose depleted, if available may be infused over 4 hours, in the dose of 1 gm/kg/day for 3 days within 48-72 hours of appearance of bullae. If 72 hours have passed, but the patient is still actively progressing with new lesions, IVIG may still be useful. (This may also be useful in situation like immunosuppressed/HIV-positive patients with TEN and in those who already have features of septicemia as IVIG is anti-infective.) The high cost of the therapy, however, is constraint to the use of IVIG in resource poor settings. Corticosteroids if used, to start in first 72 hours (prednisolone 1–2 mg/kg or dexamethasone 8–16 mg if limited surface area, given for 3–5 days and tapered off).

Antibiotic Therapy in SJS/TEN

Since most centers do not have the infrastructure for barrier nursing, prophylactic antibiotic therapy may be considered for widespread skin involvement and slightest clinical suspicion of sepsis. Empirical coverage should include one antibiotic each having anti-staphylococcal activity (amoxicillin + clavulanic acid/tetracyclines/vancomycin/clindamycin/teicoplanin/linezolid), gram-negative activity (amikacin/piperacillin + tazobactam/cefoperazone + sulbactam/imipenem), and anaerobic activity (metronidazole/tinidazole). If there is even slight suspicion that SJS/TEN has been caused by a particular antibiotic(s), it is important to strictly avoid that antibiotic group and use an alternative, structurally unrelated agent. The definite indications of antibiotic use in patients with SJS/TEN are as follows:

- High bacterial count (single strain) from skin/catheter sample of urine
- Sudden hypothermia in a relatively stable patient
- Confused mental state, anxiety, and excitement
- Symptoms of infection pertaining to a particular system; for example, pneumonia/urinary tract infection[40]

Cyclosporine in SJS/TEN (Level of Evidence II, Strength of Recommendation B)

As cyclosporin (6 mg/kg/day) inhibits CD8 cells, extensive epidermal destruction may be reduced. Furthermore, it appears to shorten the duration of active disease within 24–36 hours and time to complete re-epithelialization. It causes inhibition of CD8 cell activation, interferes with TNF-α, and is anti-apoptotic.[41] An open-label trial on 29 patients resulted in no deaths where the SCORTEN predicted death rate was 2.75.[42]

Corticosteroids in SJS/TEN (Level of Evidence II, Strength of Recommendation B)

Corticosteroids that have been used in SJS/TEN include methylprednisolone (1–2 to 4 mg/kg/day to 600–1000 mg/day), prednisolone (0.5–1 mg/kg up to 200–400 mg/day), and dexamethasone. However, studies have shown double mortality with dexamethasone over supportive therapy alone. In a case series of 44 patients, excessive mortality was reported with prolonged use of systemic steroids.[29,43] The EuroSCAR study in 2008 concluded that neither corticosteroids nor IVIG had any significant effect on mortality in comparison with supportive care only.[44] In a comparative study of corticosteroids with cyclosporin conducted in the author's department, it was concluded that cyclosporin was superior to corticosteroids in terms of reduced duration to stabilization, improved mean time to reepithelization, reduced hospital stay, and improved overall mortality, all of which were statistically significant.[45]

Combined use of corticosteroids with IVIG has been compared to the use of corticosteroids alone in a study from China. Patients on corticosteroids were 16% more likely to die than with routine supportive therapy. Those on corticosteroids plus IVIG were 15% less likely to die than with supportive treatment. The difference was not statistically significant.[46] Another study from China on similar lines suggested that early use of corticosteroids presented beneficial effects in SJS/TEN and the combination of corticosteroids with IVIG was more beneficial than corticosteroids alone.[47] A recent prospective study from India concluded that though improvement was slightly faster with IVIG, early administration of corticosteroids was also of encouraging efficacy, and should be considered in developing countries due to low cost. It also suggested the need to validate the SCORTEN in the Indian scenario in view of low mortality compared to that predicted by SCORTEN.[48]

Other Drugs in SJS/TEN (Level of Evidence III, Strength of Recommendation C)

Cyclophosphamide: Intravenous cyclophosphamide was used at 300 mg/day, tapered to 100 mg/day in 6 days with good results in a patient.[49] However, there have been some reports of cyclophosphamide-induced TEN of which one report showing positive rechallenge. In comparison, cyclosporin was found to have better results than cyclophosphamide.[50]

Plasmapheresis: It has been used as daily exchanges till 24 hours had elapsed after eruption of new blisters.[51] It has been used in patients with HIV/AIDS.[52] A preliminary report on the use of IVIG with plasmapheresis has been presented.[53]

N-acetylcysteine: It has been used at 300 mg/day and has been found to reduce time to reepithelization.[54]

Pentoxifylline: It has been used in some patients based on its role of inhibiting TNF-α.[55,56]

Dexamethasone pulse therapy: In a study performed in the Netherlands, dexamethasone was initially given as dexamethasone/cyclophosphamide pulse and later cyclophosphamide was withdrawn and patients were given dexamethasone 1.5 mg/kg for 3 days. Of 12 patients, 1 died (with a SCORTEN predicted mortality of 4). There was stabilization of lesions over 2.3 days and reepithelization over 13.9 days.[57]

Colony-stimulating factor: In a study from Denmark, filgrastim (G-CSF) was given over a 3-day period at a daily dose of 5 μg/kg subcutaneously for a patient with leukopenia along with SJS/TEN overlap. There was rapid improvement over 24 hours.[58] Another study combining CyA and G-CSF also showed improvement.[59]

Infliximab and etanercept: The use of these agents is based on elevated lesional and serum TNF-α levels in SJS/TEN. A single dose of 5 mg/kg of infliximab is used and has led to abrupt cessation of lesions. A couple of studies on use of etanercept also exist in the literature. However, these agents are not routinely used in the management of SJS/TEN as on today. Also, there has been a single case report of etanercept-induced SJS.[60]

Tacrolimus: In a case reported by the author, it has been used in the dose of 0.12 mg/kg/day for 4 days followed by tapering over 2 days. It is a cost-effective and safe treatment modality that has been found to be effective in SJS/TEN although studies in larger number of patients are needed to substantiate its therapeutic role.[61]

Role of blood transfusion: Eighteen cases (10 SJS, 8 TEN) with 60%–80% skin involvement were treated with blood transfusion. In eight patients (3 SJS, 5 TEN), systemic corticosteroid was given as they were brought within 3–4 days. All patients were given 2–3 units of blood. Two patients died and 16 had favorable prognosis.[62] The proposed mechanism of action was that toxic metabolites of the incriminating drug, namely, arene oxides, get diluted by hemotransfusion resulting in its reduced action on target tissue, for example skin and mucous membranes. In addition, cytotoxic T cells and autoantibodies could also be getting diluted. Freshly transfused blood also supplies immunoglobulins to combat infections. Transfused blood prevents hypovolemia and supplies nutrients and electrolytes essential for tissue perfusion and thereby indirectly helps in the function of cardiovascular and renal system.

Other Drugs Considerations in SJS/TEN

- Antacids, analgesics (pethidine, tramadol), and anxiolytics, if respiratory condition permits.
- Avoid grapefruit juice if cyclosporine A is used; look for sepsis and severe leukopenia.

Other Components of Therapy[63]

- Eye and oral care.
- Pulmonary care: Lung involvement may be complicated by pulmonary edema during fluid replacement. Pulmonary care includes normal saline aerosols, bronchial aspiration, and postural drainage by turning the patient to different sides. Pooling of saliva and secretions may predispose to aspiration and therefore need to be cleared frequently. Hypostatic pneumonia should be prevented by frequent change of posture and mobilization of the patient as early as possible. The nose may require attention in the form of moisturization with saline and removal of adherent crusts.
- Monitoring for complications: Acute skin failure, neutropenia, renal insufficiency, septicemia (*pseudomonas*, *Staphylococcus aureus*, gram-negative sepsis, and candida), gastrointestinal hemorrhage, and pneumonia.
- Facilities for ventilatory support, dialysis, and blood transfusion should be available.
- Anticoagulation by the use of heparin have some studies in support of utility. Early mobilization of patient is also helpful.
- The common sequelae are ocular and are needed for long-term photoprotection.

Care of Eyes

Recently, amniotic membrane transplantation was

reported to be effective in preserving visual acuity and intact ocular surface.[64,65] Topical bevacizumab (25 mg/mL) for prevention of ocular surface neovascularization have been used. Symblepharon rings have been tried and topical corticosteroids have to be instilled in the eyes.

Psychological Care

Providing emotional support and maintaining a continual dialogue with the patient and his/her family is a vital part of supportive care and addresses the patient's fears/anxieties, improves compliance with daily nursing care, and gives an opportunity for patient education about self-care after discharge and prevention of future episodes.

Monitoring of Treatment Efficacy

The increase in soluble TRAIL a TNF-α family member (upto twofold) and soluble CD200 (up to six-fold) in blister fluid may provide useful information in understanding disease pathogenesis and monitoring treatment efficacy.[66]

Clinical Risk Management

A causality assessment by use of lymphocyte transformation test should be done within 1 week of resolution of symptoms. There is no role of desensitization or rechallenge in SJS/TEN. One must ask first-degree relatives to avoid drugs of the same class as that which has caused SJS/TEN in the index patient.

The management is summarized in Fig. 30.9.

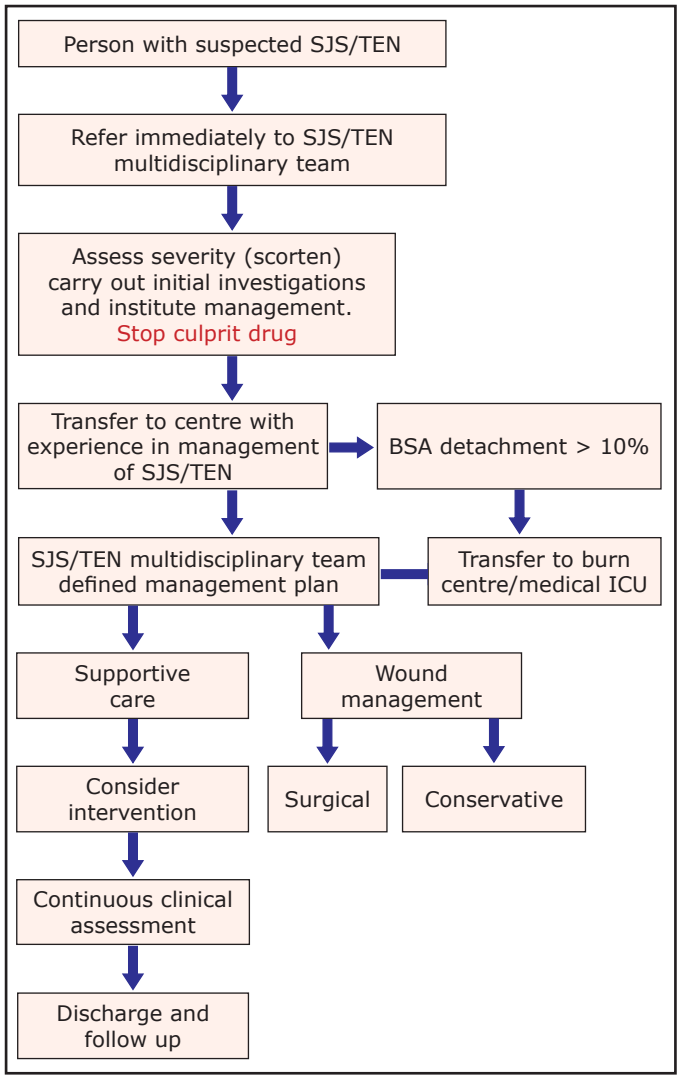

Fig. 30.9: Flowchart showing summary of management of SJS/TEN.

SJS/TEN IN THE PEDIATRIC POPULATION

Though far less common, cases have been reported after use of trimethoprim/sulfamethoxazole combination for community acquired methicillin-resistant *S. aureus* infection.[67]

Use of trypsin inhibitor: Ulinastatin was used in the management of SJS and TEN in pediatric patients.[68]

RECOMMENDATIONS[40]

Indian Association of Dermatologists, Venereologists and Leprologists (IADVL) expert group have suggested the following guidelines for the management of patients with SJS, SJS/TEN overlap and TEN:

1. Immediate withdrawal of all suspected/offending drug(s) and related compounds (strength of recommendation B).
2. Initiation of supportive therapy as the primary measure to be undertaken in all patients of SJS/TEN presenting to a health-care professional (strength of recommendation B).
3. If the rash has been identified at a primary or secondary health-care center, the treatment should be initialized and thereafter referred to a tertiary care center for care by a dermatologist.
4. If resources are available, the treatment may be carried out in an intensive care setting or in an isolated room with maintenance of sterile field. A multidisciplinary approach involving dermatologist, physician/pediatrician, ophthalmologist, respiratory physician, intensivist, dietician, and any other specialist as per the need of the case should be adopted.
5. Disease-modifying treatment must be initiated as early as possible.
6. Systemic corticosteroids (preferably parenteral) are recommended as the disease-modifying treatment of choice (strength of recommendation B). Prednisolone, dexamethasone, or methylprednisolone should be given early

(preferably within 72 hours) in high dosage (1–2 mg/kg/day prednisolone or 8–16 mg/day of dexamethasone intravenous or intramuscular). A daily assessment of disease activity (such as the appearance of new lesions, perilesional erythema, and skin tenderness) should be done and steroids should be maintained at the same dose till disease activity ceases. Thereafter, dosage should be tapered quickly such that the total duration of steroid therapy is around 7–10 days. Steroids can also be administered in pulse form using slow intravenous infusion of methylprednisolone (500–1000 mg/day) or dexamethasone (100 mg) for 3 days.

7. Cyclosporine (strength of recommendation B) can also be used alone (3–5 mg/kg/day) for 10–14 days, especially in patients with relative contraindications to corticosteroid use (e.g. patients with tuberculosis and severe hyperglycemia).
8. If both steroids and cyclosporin are used, steroids can be tapered even more quickly (2–3 days) and cyclosporin (3–5 mg/kg/day) can be continued for 7–10 days.
9. If a patient reports at a stage when the disease activity has already ceased, there is no need of any disease-modifying treatment. Such patients should be managed by supportive therapy alone.
10. Monitoring and management of complications (vital signs, signs of sepsis, and systemic involvement) and sequelae with the help of a multidisciplinary team of specialists is important.
11. In patients with HIV, children, and pregnant women in the first trimester, low-dose of IVIG (cumulative dose 0.2–0.5 g/kg) may be considered (strength of recommendation B), given in the first 24–48 hours.
12. Strict avoidance of offending/suspected/related drug(s) is necessary. A drug card should be issued to facilitate this.

CONCLUSION

The management of SJS/TEN is a therapeutic challenge to the clinical dermatologist. The creation of departmental treatment protocols for these conditions would go a long way in ensuring predictable survival and long-term improved morbidity of these patients.

LEARNING ESSENTIALS

- SJS and TEN are severe, life-threatening mucocutaneous adverse drug reactions with a high morbidity and mortality that require immediate medical care.
- Drugs are implicated in approximately 70% cases of SJS and all cases of TEN, most common being sulfamethoxazole, carbamazepine, phenytoin, and phenobarbitone.
- Other risk factors include HIV, radiotherapy, lupus erythematosus, bone marrow transplant and graft-versus-host disease, herpes simplex, mycoplasma, and renal insufficiency to name the most important.
- Extensive keratinocyte apoptosis induced by granulysin, a cationic protein, leading to sloughing and mucositis is the predominant pathogenetic mechanism as deduced at this time.
- SJS/TEN is characterized histopathologically by necrotic keratinocytes that are either disseminated or present in the form of complete epidermal necrosis.
- Painful targetoid lesions over upper trunk, proximal limbs, face evolving to blisters along with oral, ocular, and genital mucosal involvement are typical clinical manifestations of the SJS spectrum of disorders. TEN is characterized by sheets of epidermal loss following necrosis.
- Various organ involvement most common being eye complications.
- Management involves supportive, immunosuppressives and multidisciplinary approach.

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Chapter

31

Drug Reaction with Eosinophilia and Systemic Symptoms

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SUMMARY

Drug reaction with eosinophilia and systemic symptoms/drug hypersensitivity syndrome (DRESS/DHS) is a severe cutaneous adverse reaction (SCAR) with a case fatality rate of 10%–40%. The common precipitating drugs are aromatic anticonvulsants, allopurinol, lamotrigine, dapsone, minocycline, abacavir, co-trimoxazole, and salazopyrine. It can closely resemble infective, autoimmune, and neoplastic diseases. In the absence of definite diagnostic criteria, DRESS/DHS remains a diagnostic challenge. DRESS is a varying constellation of fever, rash, facial erythema, facial and/or pedal edema, systemic involvement, and eosinophilia. Absence of any one of these features does not rule out DRESS. A strong degree of suspicion is needed to arrive at an early diagnosis. Withdrawal of the offending agent and administration of systemic steroids can attain a cure on most occasions, but a delay in treatment can be fatal.

INTRODUCTION

Cutaneous drug reactions contribute to 2% of dermatological consultations and 5% of admissions and account for 0.1%–0.3% of fatalities among inpatients.[1]

Drug reaction with eosinophilia and systemic symptoms (DRESS), grouped under severe cutaneous adverse reactions (SCARs) is one of the unique and most challenging of drug reactions.

History

Chaiken et al. in 1950 described dilantin hypersensitivity in a patient who developed rash, lymphadenopathy, and multiorgan failure long after starting phenytoin.[2]

Subsequently, several other drugs were found to produce similar reaction patterns. Initially, these reactions were designated as phenytoin hypersensitivity syndrome (HSS), anticonvulsant HSS, allopurinol HSS, or dapsone HSS, based on the suspected offender,[3–6] but later it was realized that all these drugs precipitated a unique hypersensitivity reaction with variable clinical features.[7]

In 1959, Saltzstein and Ackerman reported that treatment with hydantoin and hydantoin-like drugs can lead to a syndrome resembling malignant lymphomas, characterized by lymphadenopathy, fever, exanthema, eosinophilia, and less frequently hepatosplenomegaly. Since lymphadenopathy was a fairly common manifestation in many of the affected, the term drug-induced pseudolymphoma was used.[8] In 1996, Callot et al. suggested that, there are two distinct clinical entities—drug-induced pseudolymphoma and HSS.[9] The former manifests as papulonodular or infiltrated plaques and has an insidious onset without visceral involvement. Histologically, it mimics lymphoma. The latter has an acute onset with widespread cutaneous rash, fever, enlarged lymph nodes, and multivisceral involvement. Lymphocytosis, atypical lymphocytes, eosinophilia, hepatitis, and high levels of lactate dehydrogenase are commonly noted. Histology is often nonspecific and only occasionally mimics lymphoma. Moreover, contrary to the rapid response obtained following withdrawal of the offending drug and administration of systemic steroids in drug-induced pseudolymphoma, HSS tends to have a prolonged, waxing and waning course even after removal of the culprit drug.

Bocquet et al. coined the term DRESS to denote this particular drug reaction.[10] In 1998, Sontheimer and Houpt suggested the terminology Drug Induced

Delayed Multi-Organ Hypersensitivity Syndrome (DIDMOHS) to describe the drug hypersensitivity with systemic involvement.[11] Terms like *Kawasaki-like syndrome* or *infectious mononucleosis-like syndrome* were also used to denote similar drug-induced constellations of symptoms, but did not find much acceptance.[12]

There is still no consensus regarding the most suitable term to describe this reaction pattern. None of the existing terminologies fully reflect the nature of this adverse reaction probably due to the widely variable clinical features. Bocquet el al. opined that the term HSS is not appropriate for a specific reaction pattern since hypersensitivity contributes to most of the idiosyncratic drug reactions and DRESS is a better terminology.[13]

Peyriere et al. was of the opinion that the acronym DRESS is not appropriate since it over emphasizes eosinophilia.[14] DIDMOHS is considered misleading and confusing since a significant percentage of DRESS patients do not develop multiorgan involvement.

Current terminologies accepted by the international study group on adverse drug reactions are HSS or DRESS.[15]

Epidemiology

The incidence of drug hypersensitivity syndrome (DHS)/DRESS is stated to vary between 1:1000 and 1:10,000 drug exposures.[16] The common drugs implicated are aromatic anticonvulsants, allopurinol, sulfasalazine, dapsone, and nevirapine.[17] Previous reports identify anticonvulsants and allopurinol as the main offenders in adults and antibiotics as the common culprits in children.[18] A study on DRESS in pediatric age group by us documented anticonvulsants as the major offender in children as well.[19] Recent years have witnessed a sharp rise in DRESS with more and more drugs being implicated as potential offenders (Box 31.1).[17,20] Whether there is an actual rise in the incidence of DRESS or whether it is a reflection of the increased awareness leading to prompt diagnosis and reporting remains unclear.

Though several decades have passed since its original description, DHS/DRESS remains an enigma. It differs from all other drug reactions known till date (Box 31.2).[12,15,16,21] Typical DHS/DRESS closely mimics many infective, autoimmune, and neoplastic diseases.[12] Its variable clinical features and lack of reliable diagnostic criteria makes it a diagnostic challenge.

The mortality rate varies from 10% to 40% in DRESS. Existing data predict long-term sequelae in nearly 12% of the affected. Autoimmune thyroid disease is the most common long-term complication observed in the young whereas in the elderly, it is renal failure requiring hemodialysis.[7]

Box 31.1: Common drugs precipitating DRESS/DIHS

- Abacavir
- Allopurinol
- Amoxicillin-clavulanic acid
- Aromatic anticonvulsants
- Aspirin
- Captopril
- Cefadroxil
- Celecoxib
- Chloroquine
- Clopidogrel
- Co-trimoxazole
- Dapsone
- Imatinib
- Lamotrigine
- Minocycline
- Nevirapine
- NSAIDs
- Spironolactone
- Sulfasalazine
- Vancomycin

NSAID - nonsteroidal anti-inflammatory drug; DRESS - drug reaction with eosinophilia and systemic symptoms; DIHS - drug-induced hypersensitivity syndrome.

Source: Cacoub et al.[17]

Box 31.2: Unique features of DRESS compared to other drug reactions

- Long latent period between onset of drug intake and appearance of symptoms
- Less severe involvement of skin and mucosae compared to other severe drug reactions
- Higher risk of systemic involvement
- Paradoxical flare up on withdrawal of the offending drug
- Requirement of prolonged treatment with systemic steroids so as to prevent flare ups
- Autoimmune manifestations in later life

DRESS - drug reaction with eosinophilia and systemic symptoms.

DIAGNOSTIC CRITERIA

Over the years, several diagnostic criteria were proposed for DRESS, but were found lacking in sensitivity or specificity or both (Table 31.1).[10,22,23]

Bocquet et al. Criteria

Bocquet et al. criteria (Table 31.1) though highly specific, lacks sensitivity to diagnose DRESS.[10] Eosinophilia is a variable feature seen in 50%–90% of cases; even when present, significant number of the patients will show eosinophilia in the range 750–1500 cells/mm^3.[7,16,20,21] So any criteria requiring eosinophilia ≥1500 cells/ mm^3 as a mandatory feature is likely to miss many cases of DRESS. Another drawback is its insistence on cutaneous eruption. Though rare, DRESS can manifest without rash.[17,20] The initial expansion of DRESS as described by Bocquet et al. was drug rash with eosinophilia and systemic symptoms. But the variability of skin involvement was subsequently recognized and "R" in DRESS was changed from "rash" to "reaction."[7,15]

The RegiSCAR Study Group Criteria[22]

These criteria suggest that the presence of three of the four systemic features in a hospitalized patient with drug reaction points to DRESS (Table 31.1).

Using this criteria, one is less likely to miss a case of DRESS, which makes it highly sensitive; but it lacks specificity since many cases of other SCARs also manifest with fever, lymphadenopathy, and systemic and/or hematological abnormalities. Fever, rash, lymphadenopathy, systemic involvement, lymphocytosis, and thrombocytopenia are well-known features of many viral exanthema and certain hematological malignancies. Though a pruritic rash is often considered a feature of drug reaction rather than a viral infection, relying too much on one subjective symptom can lead to misdiagnosis.

Japanese Consensus Group Criteria[23]

Japanese Research Committee on severe cutaneous adverse reaction (J-SCAR) in 2006 suggested that the term "drug-induced hypersensitivity syndrome (DIHS)" be used instead of DRESS since not all DRESS cases manifest eosinophilia. They proposed the Japanese consensus group criteria to diagnose DIHS (Table 31.1).

These criteria have many limitations. Though anticonvulsants are the major offenders in DRESS, newer and newer drugs are being recognized as inducers. By restricting diagnosis of DRESS to reactions precipitated by certain drugs alone,

Table 31.1: Different diagnostic criteria for DRESS/DIHS

Bocquet et al. criteria[10]	RegiSCAR study group[22] criteria for DRESS	Criteria proposed by Japanese consensus group for DIHS[23]
1. Cutaneous drug eruption 2. Adenopathies ≥2 cm in diameter, hepatitis (alanine transaminase ≥2 times the upper limit of normal), interstitial nephritis, interstitial pneumonitis, or carditis 3. Hematologic abnormalities: Eosinophilia ≥1500 cells/mm^3 or atypical lymphocytes **All three should be present to diagnose DRESS.**	1. Acute skin rash 2. Fever >38°C 3. Enlarged lymph nodes at a minimum of two sites 4. Involvement of at least one internal organ 5. Blood count abnormalities a. Lymphocytes above or below normal limits b. Eosinophils above the laboratory limits c. Platelets below the laboratory limits **Any three in a hospitalized patient with suspected drug reaction is indicative of DRESS.**	1. Maculopapular rash developed >3 weeks after starting treatment with a limited number of drugs 2. Prolonged clinical symptoms after discontinuation of the causative drug 3. Fever (38°C) 4. Liver abnormalities (Alanine transaminase >100 U/L)/other organ involvement like renal involvement 5. Leukocyte abnormalities (at least one present) a. Leukocytosis (>11,000 cells/mL) b. Atypical lymphocytosis (>5% in peripheral smear) c. Eosinophilia (>1500 cells/mL) 6. Lymphadenopathy 7. HHV-6 reactivation **If all seven criteria present—typical DIHS. All except six and seven present—atypical DIHS.**

DIHS - drug-induced hypersensitivity syndrome; DRESS - drug reaction with eosinophilia and systemic symptoms; HHV-6 - human herpesvirus 6.

Source: Bocquet et al.[10]; Kardaun et al.[22]; Shiohara et al.[23]

one might miss several similar cases. The clinical features of DRESS are quite variable. Different patients show varying combinations of fever, rash, lymphadenopathy, systemic involvement, and hematological abnormality. Insisting on the presence of all these features to diagnose DIHS, many DRESS cases would again be excluded. In addition very few centers have the facility to test for reactivation of human herpesvirus-6 (HHV-6). This prevents the wider application of these criteria. In addition, not all DRESS cases manifest HHV-6 reactivation. HHV-6 reactivation in the setting of DRESS predicts a severe (at times fatal) illness with prolonged course characterized by waxing and waning.[16,21,24] The current consensus is that DIHS is a severe form of DRESS and the former terminology should be restricted to DRESS with HHV-6 reactivation only.[16]

RegiSCAR DRESS Validation Scoring[22,25]

This scoring is based on the inclusion criteria suggested by RegiSCAR study group (Table 31.2). Patient will be considered as a suspected case of DRESS if he/she satisfies the RegiSCAR inclusion criteria and then a scoring system is used to determine whether the included case is DRESS or not.

Table 31.2: RegiSCAR DRESS validation scoring

Clinical and laboratory features	Do not add or reduce any points	Add one point	Add two points	Reduce one point
Rash		Rash involving >50% of body surface area/ rash suggestive of DRESS	Rash involving >50% of body surface area and rash suggestive of DRESS	Skin rash not suggestive of DRESS
Fever	Fever >38°C			Absence of fever
Lymphadenopathy	No lymph node enlargement	Palpable lymph nodes over 1 cm in at least two different anatomic locations.		
Involvement of internal organs	No internal organ involvement	Involvement of one internal organ	Involvement of two or more internal organs	
Eosinophilia	Eosinophil count within normal limits	Eosinophilia 750–1499 cells/mm^3 or 10%–19% if total count is below 4000 cells/mm^3	Eosinophilia ≥1500 cells/mm^3 or >20% if total count is below 4000 cells/mm^3	
Atypical lymphocytes	No atypical lymphocytes in peripheral smear	Atypical lymphocytes in peripheral smear		
Evaluation of other potential causes Antinuclear antibody Blood culture Serology for HAV/HBV/HCV Chlamydia/mycoplasma	If the mentioned tests positive or results unknown or if these tests not performed.	If none of the performed tests positive and ≥3 of the tests are negative		
Skin biopsy	Not performed or result unknown or biopsy suggestive of DRESS			If biopsy fit any other specific dermatopathologic diagnosis.
Disease course	Not resolving before 15 days			Resolution within 15 days

DRESS - drug reaction with eosinophilia and systemic symptoms; HAV - hepatitis A virus; HBV - hepatitis B virus; HCV - hepatitis C virus.

Note: Rash suggestive of DRESS is defined as rash having two of the four features—purpuric lesions on areas other than legs, facial edema, infiltrated lesions, rash subsiding with psoriasiform desquamation.

Final scores: <2 DRESS excluded: 2–3 possible DRESS; 4–5 probable DRESS; >5 definite DRESS.

Source: Kardaun et al.[22]; Chen et al.[25]

Assessing Internal Organ Involvement in DRESS as per the RegiSCAR Scoring System

Points for internal organ involvement in DRESS should be calculated only after ruling out other causes which can produce similar changes (Table 31.3).[25]

Table 31.3: Internal organ involvement in DRESS

Internal organ affected	Criteria
Liver (any one criteria)	Alanine transaminase >2 times the upper limit of normal limits twice on successive dates or Direct bilirubin >2 times the upper limit of normal limits twice on successive dates or Aspartate transaminase, total bilirubin, alkaline phosphatase all >2 times the upper limit of normal limits, once
Kidney (any one criteria)	Creatinine >1.5 times the patient's baseline on at least 2 successive dates or Proteinuria >1 gm/day, hematuria, decreased creatinine clearance, or decreased glomerular filtration date
Lungs (any one criteria)	Evidence of interstitial lung disease on CT or X-ray or Abnormal bronchoalveolar lavage fluid or biopsy specimen or Abnormal blood gases
Muscle/ Heart (any one criteria)	Raised serum CPK >2 times the upper limit of normal or Raised isoenzymes fraction: CPK-MM (skeletal muscle), CPK-MB (heart muscle) or Raised troponin T >0.01 μg/L or Abnormal imaging, including chest X-ray, echocardiogram, electrocardiogram, electromyogram, CT, or MRI
Pancreas	Amylase and/or lipase >2 times the upper limit of normal
Others	Spleen, thyroid gland, central nervous system, gastrointestinal tract

MRI - magnetic resonance imaging; CT - computed tomography; CPK - creatine phosphokinase

Source: Chen et al.[25]

The advantage of RegiSCAR DRESS validation scoring system is that it takes into account the fact that DRESS is a multisystem disease; but does not forget to consider its variable clinical features. This is an ideal one for study purposes for recruiting cases. The major disadvantage is its inability to diagnose DRESS at the time of presentation since all clinical and laboratory features may not be present at the onset of disease and may not be present together. Moreover, this scoring system takes into consideration variables like time taken for the disease resolution which will not be available on the day of hospitalization.

In other words, DRESS remains a diagnosis of exclusion and a high degree of suspicion is needed to arrive at a prompt diagnosis which is very crucial as a delay in withdrawal of the offending drug can prove fatal.

PATHOGENESIS

Exact pathogenesis of DRESS/DHS remains elusive; the most accepted postulate suggests that DRESS results from a complex interaction between the drug or its metabolites with the immune system of susceptible individuals, which at times is complicated by the reactivation of certain herpes family of viruses, usually HHV-6 or 7, Epstein–Barr virus (EBV), or cytomegalovirus (CMV).[16,23,26–28]

Role of Genetic Factors in DRESS/DHS

The development of drug hypersensitivity depends on genetic and environmental factors. Role of genetic factors in precipitating drug hypersensitivity is illustrated by specific human leukocyte antigen (HLA) associations documented in certain drug reactions especially Steven–Johnson syndrome/ toxic epidermal necrolysis (SJS/TEN)/DRESS.[29–33] HLA associations placing a patient at greater risk for severe drug reactions are not surprising since the former play a crucial role in T-cell stimulation. Many authors proposed that DRESS is mainly a type IVb hypersensitivity reaction, with Th2-type immune response and eosinophil activation.[7]

The Hapten Theory and pi Concept

Role of HLA molecules in severe drug reactions such as DRESS is better explained by the hapten theory and pi concept.

According to the *hapten theory*, small, immunologically neutral molecules become antigenic by binding to a protein after they get metabolized by detoxification enzymes.[33,34] For example, sulfamethoxazole forms haptens after it is metabolized to nitroso sulfamethoxazole.[33,35]

pi concept proposes that a drug can stimulate

T cells in a HLA-dependent manner without forming haptens. This occurs when a chemically inert drug directly react with T-cell receptors or major histocompatibility complex (MHC) molecules.

Ultimately in both instances, the expanded T cells mediate the immune response.

One prime example of HLA-dependent stimulation of T cells by a drug is the association of abacavir hypersensitivity with HLA-B*57:01 allele. People carrying this allele have a 50% chance of developing abacavir HSS. Hence it is recommended that before initiating treatment with abacavir, the presence of HLA-B*57:01 should be excluded.[33,36]

It is believed that noncovalent binding of abacavir changes the self-peptide loading onto HLA-B*57:01 molecules. This leads to display of new endogenous peptides on the cell surface of antigen presenting cells, which in turn initiate a polyclonal T-cell response to self-epitopes. The altered peptide repertoire explains the autoimmune manifestations reported following DRESS.[33]

Similarly, it is advocated to carry out screening for HLA-B*15:02 in Asian population before commencing treatment with carbamazepine but this association is not as strong as the one between abacavir and the respective HLA variant. HLA-B*15:02 allele is associated with carbamazepine-induced SJS/TEN in Han Chinese. Japanese and European studies were indicative of an association between HLA-A*31:01 and drug hypersensitivity including SJS/TEN, DRESS, and maculopapular exanthema to carbamazepine.[31,33]

Another noted HLA association is between HLA-B*58:01 allele and allopurinol-induced SJS/TEN and DRESS.[32,33]

Role of Reactive Metabolites

Aromatic Anticonvulsants

Reactive drug metabolites are mainly implicated in DRESS induced by aromatic anticonvulsants such as phenytoin, phenobarbitone, and carbamazepine. The parent drugs are metabolized by cytochrome P450 to arene oxide radicals. The resultant toxic metabolites are further detoxified by epoxide hydroxylase and glutathione transferase. Patients genetically lacking these enzymes or having defective enzymes are prone to develop DRESS.[12,16,21]

Hapten hypothesis postulates that the toxic metabolites form immunogens or produce neoantigens after binding to tissue macromolecules. Another theory put forth is the danger hypothesis which suggests that the oxidative damage precipitated by the reactive drug metabolites leads to cytokine release. This in turn facilitates an immune response.[12] The documented cross-reactivity between various aromatic anticonvulsants range from 40% to 80%.[16]

Lamotrigine

Lamotrigine is a broad-spectrum antiepileptic mainly metabolized in liver via glucuronidation. Minor amounts are converted by cytochrome P450 (CYP) enzymes to arene oxide intermediates.[37]

Half-life of lamotrigine is shortened in the presence of hepatic enzyme inducers such as phenytoin, carbamazepine, phenobarbital, and primidone and to a lesser extent by oxcarbazepine, whereas coadministered valproic acid lengthens its half-life. In children, the glucuronide conjugation is reduced and CYP-mediated reactions are accelerated compared with adults, resulting in the increased production of reactive arene oxides.[37,38]

Lamotrigine is well known to produce benign and serious cutaneous adverse reactions including DRESS. As per available data (including one of our studies), the risk of adverse reaction to lamotrigine depends on the coadministered drugs (more with sodium valproate), dose (greater risk at higher dose) and on the rate of upward titration of lamotrigine (higher risk with faster titration to therapeutic dose).[19,37,39]

Hence it is recommended to start lamotrigine at a small dose and gradually titrate over several weeks or months to the desired therapeutic level (Table 31.4).[39] Adhering to this guideline has dramatically reduced the incidence of lamotrigine-induced drug reactions including DRESS.[37]

Allopurinol

Chronic renal insufficiency and a higher dose of allopurinol are found to be independent risk factors for allopurinol-induced SCAR. This is attributed to the generation of more drug-specific T cells by the higher serum levels of allopurinol or its metabolite oxypurinol.[33,40,41]

Role of Herpes Family of Viruses in DRESS/DHS

Viral infections are well-known risk factors for drug reactions. The higher incidence of adverse reactions in human immunodeficiency virus (HIV)-positive individuals is cited as an evidence of impact of viral infections in drug reactions.[42] The proposed mechanisms are the virus-induced alterations in self-antigens that are perceived as neoantigens by the body and the subsequent immune activation and the virus-induced immune dysregulation.[43]

Table 31.4: Recommended initial dosage and titration for lamotrigine

Treatment regimen	Weeks 1–2		Weeks 3–4		Week 5 onwards till achievement of maintenance dose		Maintenance	
	2–12 years	>12 years	2–12 years	>12 years	2-12 years	>12 years	2–12 years	>12 years
With valproic acid	0.15 mg/kg/day	25 mg alternate days	0.3 mg/kg/day	25 mg once daily	Increase by 0.3 mg/kg/day every 1-2 weeks	Increase by 25 -50 mg/day every 1-2 weeks	1–5 mg/kg/day	100–200 mg/day
Monotherapy	0.4 mg/kg/day	25 mg once daily	0.8 mg/kg/day	25 mg twice daily	Increase by 0.8 mg/kg/day every 1-2 weeks	Increase by 50 mg/ day every 1-2 weeks	2–8 mg/kg/day	100–400 mg/day
With inducing antiepileptic drugs	0.6 mg/kg/day	50 mg once daily	1.2 mg/kg/day	50 mg twice daily	Increase by 1.2 mg/kg/day every 1-2 weeks	Increase by 100 mg/ day every 1-2 weeks	5–15 mg/kg/day	300–500 mg/day

Note: Inducing antiepileptic drugs are carbamazepine, phenytoin, phenobarbitone, etc.

Source: Zaccara et al.[37]; Werz[38]; Bourgeois[39]

It was always considered that viral infections could play a major role in precipitating DRESS. The long latent period between the onset of drug intake and DRESS, its clinical resemblance to viral infections (especially infectious mononucleosis), paradoxical flare-ups noted soon after withdrawal of the offending drug and waxing and waning disease course—all pointed to a probable viral etiology.

So it was not surprising when in 1997 Descamps et al. reported evidence of HHV-6 reactivation in a patient with phenobarbitone-induced DRESS.[26] HHVs are ideal candidates to precipitate DRESS considering their ability to produce latent infection, tendency to persist in lymphocytes, and their propensity to undergo reactivation.

HHV-6 is a lymphotropic DNA virus with two genetic variants HHV-6A and 6B. In majority of the population, HHV-6B infection occurs within the first 2 years of life after which it remains latent in salivary glands, peripheral blood mononuclear cells, and the central nervous system. HHV-6 reactivation is well reported in immunosuppressed individuals where it manifests with fever, rash, encephalitis, and bone marrow suppression.[44] But the exact role played by HHV-6 in DRESS remains to be elucidated. One theory put forth is the increased production of reactive drug metabolites induced by the viral reactivation leading to DRESS.[7,15]

HHV Reactivation: A Secondary Event in DIHS?

Some suggest that the drug or its metabolites activates the T cells and this in turn reactivate the latent HHV-6 genome in T cells. Drug metabolites stimulate monocytes and macrophages (the reservoirs cells of latent HHV-6) to secrete interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). The resultant "cytokine storm" is believed to play an important role in viral reactivation.[16,21,45]

It is also documented that in acute stage of DRESS, there occurs an expansion of regulatory T cells; but they lose their function during the phase of resolution of DRESS. It was suggested that the delay in onset of symptoms and the proposed viral reactivation in DRESS/DIHS reflect the suppression of activation of effector T cells by the expanded regulatory T cells.[16,21,45]

Moreover drugs such as amoxicillin and sodium valproate can induce replication of HHV-6 in vitro.[46] Sodium valproate is known to favor replication of cytomegalovirus (CMV) as well. It is believed that valproic acid exerts its effect on herpes viruses through inhibition of histone deacetylase.[47]

Some authors suggest that the viral reactivation is due to the immunosuppression induced by the systemic steroids given for managing DRESS.[44] But the lack of herpes virus reactivation in many of the DRESS cases treated with steroids does not favor this hypothesis of systemic steroids precipitating viral reactivation.

Is HHV Reactivation the Primary Event in DIHS?

Kano et al. suggested that HHV-6 reactivation is the cause rather than an effect of DIHS.[48] According to them, certain drugs induce transient immuno-

suppression resulting in reduced immunoglobulin production. What exactly induces this immunosuppression remains unclear. It is proposed that a reduction of plasmacytoid dendritic cells in the peripheral circulation leads to reduced immunoglobulin production by affecting the B-cell maturation and subsequent production of immunoglobulins.[7] This immunosuppression allows HHV-6 to reactivate from latency in the presence of drug-specific T cells. The long latent period in DRESS/DIHS is attributed to the time taken for the immunoglobulin levels to fall below a certain limit.[48]

DRESS/DIHS—An Immunological Paradox

DRESS/DIHS differs from other drug reactions by the sudden shift in the immune response noted during the course of the disease. It is documented that total serum IgG, IgA, IgM, and B lymphocytes fall at the onset of DRESS, whereas memory T cells cross-reacting with both the drug and the virus show a rise. At the onset of DRESS, there occurs an expansion of CD4+ CD25+FOXP3 (regulatory) T cells with CCR4+ CLA+ phenotype that is associated with skin. It is believed that circulating CD4+ T cells change from CD4+ to CD8+ phenotype during DRESS.[7,16,21,48]

The number of regulatory T cells increase in the skin, but decrease in the organs that manifest a functional deterioration. It is observed that pro-inflammatory cytokines such as TNF-α and IL-6 are elevated before the reactivation of HHV-6. The level of IL-6 fluctuates during the course of disease. It shows a rise before HHV-6 reactivation becomes undetectable during viral replication and again shows a rise after the viral infection in majority of patients.[7,16,21,48]

Reason for the Less Severe Cutaneous Involvement in DRESS/DHS

Though both are SCARs, DRESS shows major differences from SJS/TEN. One of the most important differentiating feature is the less severe involvement of skin and mucosae in DRESS. The cutaneous necrosis and mucosal sloughing, the hallmark of SJS/TEN, are not observed in DRESS. This is attributed to the expansion of regulatory T cells noted in the acute stage of DRESS which in turn suppress the T-cell-mediated inflammatory response. In TEN, the ability of regulatory T cells to migrate to the skin to suppress the activation of cytotoxic T cells is impaired, despite their presence in normal quantities in blood.[21]

Causes of Multiorgan Failure in DRESS/DHS

Multiorgan failure is more common in DIHS.[49] Superadded bacterial infection and hemophagocytosis are also cited as causes for multiorgan failure in DRESS. Hemophagocytosis is thought to be precipitated by the massive immune dysregulation associated with DRESS leading to increased production of interferon γ and macrophage colony stimulating factor.[26]

Pathogenesis of Waxing and Waning Course in DRESS/DHS

Descamps et al. in 1997 reported a possible role for HHV-6 infection in inducing DRESS. Since then many authors supported this theory and it was documented that the herpes virus association predicted a severe form of DRESS with internal organ involvement and recurrent flare-ups requiring prolonged treatment and at times resulting in fatal out comes.[16,21] We have reported a severe form of DRESS induced by carbamazepine with disease flares. Subsequent demonstration of HHV-6 reactivation confirmed it as DIHS.[50] Aihara et al. in 2001 described evidence of CMV reactivation in a patient with phenytoin-induced HSS.[27] In 2002, Descamps et al. documented EBV infection in allopurinol-induced HSS with pancreatitis.[28] It is suggested that the expansion of regulatory T cells in the beginning of DIHS/DRESS prevents activation of antiviral T cells leading to sequential reactivation of herpes viruses.[7,21,51]

Shiohara et al. reported that the varying clinical manifestations and the waxing and waning course of DRESS is attributed to sequential reactivations of several herpes viruses, irrespective of the treatment received.[21] Kano et al. reported that in DIHS, reactivation of HHV-6 (2–3 weeks after the onset of symptoms) and EBV takes place in the early phase followed by those of HHV-7 and CMV. It is suggested that HHV-6 and CMV infect T cells latently.[51] EBV infects B cells alone. It plays a role in DIHS by amplifying the drug-induced T-cell activation.[28]

Tapering the dose of steroids is often associated with disease flares probably due to the amplification of immune response against viruses.[20,49] Most of the flares induced by steroid taper could be controlled by increasing the dose of systemic steroids and opting for a slower taper.[20]

Another factor found to precipitate exacerbation during the course of DRESS is introduction of a new drug before resolution of DRESS. Pichler et al. described that during a severe drug reaction, in the milieu of immune activation, patient may develop hypersensitivity to a coadministered, previously well-tolerated drug leading to exacerbation of the existing reaction pattern or manifestation of a different drug reaction. The allergy to the second drug may be transient when it is termed as flare-up reaction or permanent when it is designated as multiple drug allergy syndrome.[43]

Mardivirin et al. reported that amoxicillin, when given during DRESS induced by other drugs, may precipitate a flare. They demonstrated it to be the outcome of direct action of amoxicillin on herpesvirus replication. It is recommended to keep the number of drugs given during treatment of DRESS to an essential minimum.[43,46]

Autoimmune Manifestations following DRESS/DHS

One of the unique features of DRESS is the appearance of autoimmune manifestations following resolution of DRESS. Exact cause for the autoimmune manifestations that follow DRESS remains unknown. The time interval between DRESS and the autoimmune events vary from months to years so that at times the possible link between the two goes unrecognized. It is postulated that the regulatory T cells that are expanded during the acute stage of DRESS become dysfunctional after resolution of DRESS, placing the recovered patients at an increased risk for developing autoimmune diseases later in life.[7,16,45]

Viral Reactivation with Eosinophilia and Systemic Symptoms

This recently described terminology suggests that viral reactivation (mostly herpes viruses) itself can produce symptoms described in DRESS. To distinguish between the drug-induced reaction pattern and the viral reaction pattern, the term viral reactivation with eosinophilia and systemic symptoms (VRESS) has been proposed. HHV-6 reactivation by itself can manifest as multiorgan failure syndrome.[44] There are reports of disseminated HHV-6 primary infection in infancy, childhood, and in immunocompromised individuals resulting in multiorgan failure.[44] This strong antiviral immune response (independent of DRESS) leading to multiorgan failure is termed as the "DRESS picture".[52]

It is suggested that some of the cases reported as highly active antiretroviral therapy (HAART)-induced DRESS in HIV positive patients could be VRESS reflecting herpes virus reactivation as an immune reconstitution inflammatory syndrome (IRIS). Regulatory T cells are known to play a role in both DRESS and VRESS. VRESS is reported in scenarios of IRIS with HHV reactivation like HIV patients after the initiation of HAART, transplant recipients (usually 3 weeks after transplantation), graft versus host disease or in patients in intensive care units. In these situations, immunosuppression may cause the viral reactivation; but only those who are able to mount a strong antiviral immune response manifest the clinical features.[52,53]

VRESS is also characterized by paradoxical disease flares, which is attributed to the strong antiviral immune response. This justifies the combined treatment with antivirals and corticosteroids or immunosuppressants.[52,53]

In the first phase of both DRESS and VRESS, gradual increase in herpes virus reactivation takes place. This has led to the suggestion that if common inducers of DRESS like allopurinol, sulfasalazine, or anticonvulsants are initiated at a small dose and gradually increased to the therapeutic level, the chances of herpes virus reactivation and possibly the risk of adverse drug reactions could be reduced. A slower introduction and gradual titration has shown to be of use in reducing serious drug reactions induced by lamotrigine! [In addition, we suggest that the risk of DRESS can be reduced by avoiding drugs such as amoxicillin (which can promote herpes virus replication) during the initial weeks of treatment with drugs that are well known to induce DRESS/DIHS.][46] In the second phase of both DRESS and VRESS, a strong antiviral immune response is elicited, which could be genetically predisposed (as in DIHS) or could be precipitated by a state of IRIS or graft versus host disease (in VRESS).

Third phase is marked by the DRESS or VRESS flares. This is attributed to a faster reduction of steroid or antiviral treatment in DRESS and VRESS respectively. This necessitates the need for tapering based on viral load. But due to the lack of facility to determine viral load in most of the centers, the second best option would be careful tapering of systemic steroids and a prompt increase in dose on evidence of flares.[20]

A complex interaction occurs between the drug, herpes virus and the genetically predisposed individual's immune system in DRESS/DHS. Future studies may yield further information on the several unknown aspects of this SCAR.

CLINICAL MANIFESTATIONS[14,18,20,54–57]

The mean age of the affected persons vary from 37 to 57 years in various studies (Table 31.5). Though rare, there are occasional reports of DRESS in children including infants.[19,20,54–58] Diagnosis becomes extremely challenging in children since many viral exanthems, commonly seen in pediatric age group including EBV infection can closely mimic DRESS. Kawasaki disease, another close differential diagnosis of DRESS is mainly seen in preschool children [59–61] Compared to adults, DRESS in children show a faster and full recovery.[19,62]

Most of the studies show a female predominance.[18,20,54,56,57] The usual time interval between the onset of drug intake and appearance of symptoms

Table 31.5: Features of DRESS noted in various studies

Features of DRESS	Peyriere et al. (France)[14] (1985–2000)	Chen et al. (N Taiwan)[54] (1998–2008)	Chiou et al. (Taiwan)[55] (2001–2006)	Ang et al. (Singapore)[18] (2003–2008)	Um et al. (S Korea)[56] (2004–2009)	Hiransuthikul et al. (Taiwan)[57] (2004–2014)	Sasidharanpillai et al. (India)[20] (2010–2013)
No of patients	216	60	30	27	38	52	26
Common offenders	AAC, Abacavir	Allopurinol	Allopurinol	AAC	AAC	Phenytoin	AAC
Mean age	NA	51	51	51	56	33	37
Male:Female	1.5:1	1:1.3	1:1	1:1.25	0.9:1	0.4:1	0.9:1
Fever (%)	69	87	72	78	100	79	96
Rash (%)	100	100	100	100	100	100%	96
Most common type of rash	Exanthema-tous	Exanthema-tous	Exanthema-tous	Exanthema-tous	NA	Exanthematous	Exanthematous
Lymphadenopathy (%)	18	31	50	NA	53	50	50
Hepatic involvement (%)	52	80	87	96	100	94	81
Renal involvement (%)	10	40	53	15	16	15	8
Eosinophilia	57	52	48	82	92	58	88
Atypical cells in peripheral smear	7	63	45	15	47	30	19
Mortality rate	10–40	10	10	0	3	4	4

AAC - aromatic anticonvulsants.

Source: Peyrie`re H et al.[14]; Ang et al.[18]; Sasidharanpillai et al.[20]; Chen et al.[54]; Chiou et al.[55]; Um et al.[56]; Hiransuthikul et al.[57]

vary from 1 week to 3 months.[12,16,21] But can be as early as 3 days or as late as 2 years.[8,18,54–56] A longer incubation period has been noted for carbamazepine- and allopurinol-induced DRESS.[12,20,63]

The common features of DRESS are fever, rash, facial and/or pedal edema, lymphadenopathy, elevated liver transaminases, eosinophilia, and atypical lymphocytes in peripheral smear.[7,12,15,16,21] Different patients show varying combinations of these clinical features. A strong suspicion is needed to make the correct diagnosis at the right time.

Fever

Incidence of fever in DRESS vary from 70% to 100%.[14,18,20,54–57] Quite frequently it is the initial symptom (at times accompanied by sore throat) for which the patient gets treated with antipyretics and/or antibiotics. So when a rash appears within the next couple of days (which is the normal course in DRESS), the antibiotic or antipyretic prescribed is considered as the culprit. When withdrawal of the same and administration of antihistamines and/or systemic steroids does not bring a relief, the clinician may be misled. A detailed history of drug intake prior to the onset of the initial symptom which could be fever/rash/internal organ involvement may enable the treating clinician to suspect the offender. It is of paramount importance to remember that the initial symptom in DRESS could be fever.

Rash

Cutaneous rash is a universal finding though there are occasional reports of DRESS without rash.[14,16–18,20,64,65] It is noted that DRESS without rash manifests in those who are receiving prednisolone in a dose of 10 mg/day or more along with another immunosuppressive agent and in those with HIV infection.[64,65] We have observed DRESS without rashes in two patients.[19,65]

The most common rash observed in DRESS is maculopapular (Fig. 31.1) followed by diffuse erythematous type (Fig. 31.2) and exfoliative dermatitis (Fig. 31.3).[16,20,21,54–57] It often starts on the face, upper trunk, or extremities and then extends to involve most of the body.[12,21] (All our DRESS patients with rash, gave history of rash starting on the upper chest or forearm followed by facial edema and subsequent generalization). Sparing of distal extremities has been documented in some cases.[20] Dermal edema producing follicular accentuation eventually leading to formation of infiltrated plaques is a characteristic feature of DRESS (Fig. 31.4).[12,25] Severe dermal edema may induce blister formation in skin.[7,21] Absence of cutaneous necrosis distinguishes the bullous lesions of DRESS from that of TEN.[7]

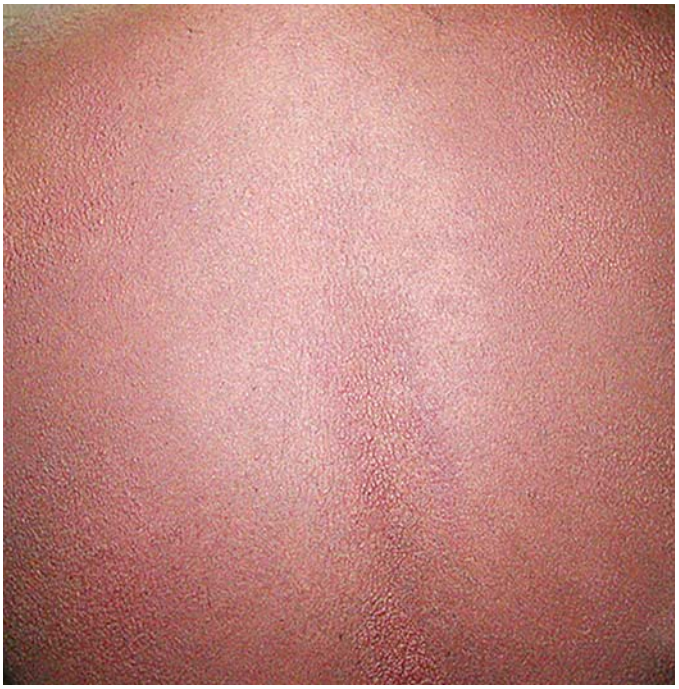

Fig. 31.1: Maculopapular rash of drug reaction with eosinophilia and systemic symptoms (DRESS) in a patient on co-trimoxazole for urinary tract infection.

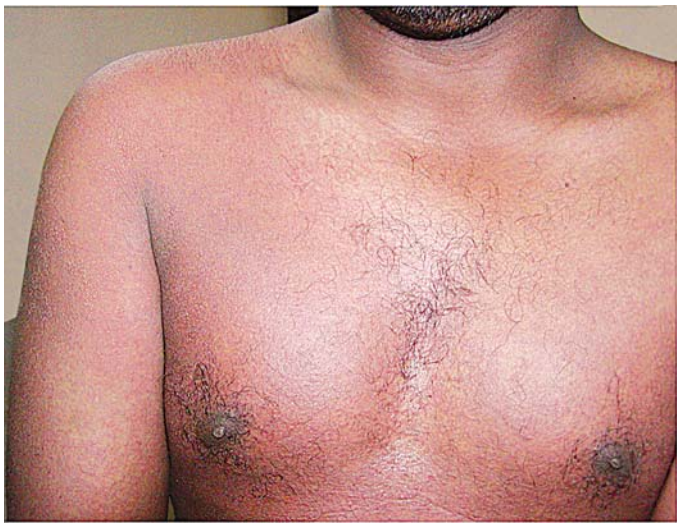

Fig. 31.2: Diffuse erythematous rash of DRESS in a 32-year-old man on phenytoin for seizures.

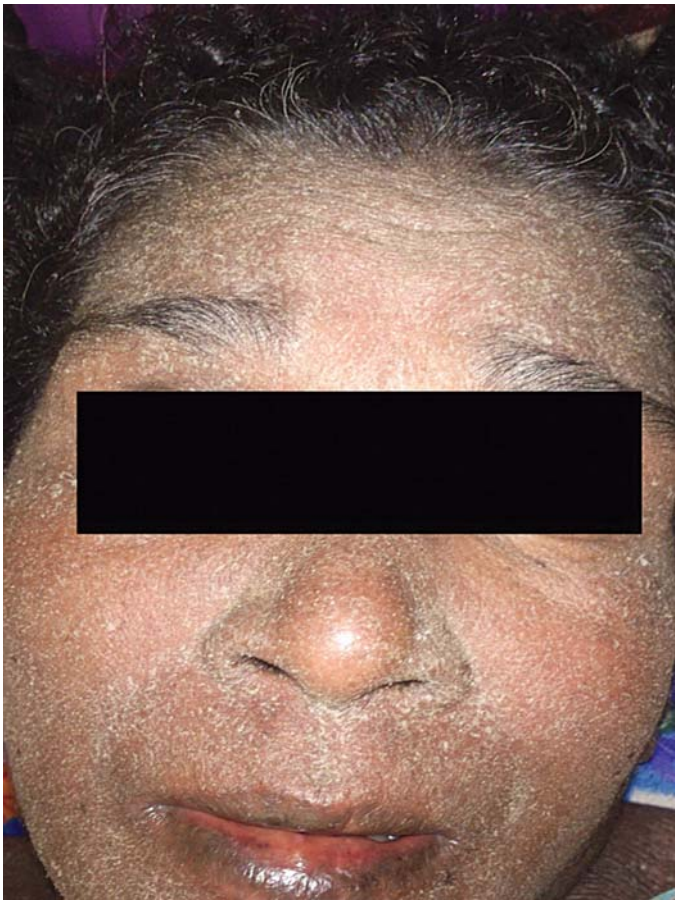

Fig. 31.3: Rash of DRESS manifesting as exfoliative dermatitis 6 weeks after starting dapsone in a patient of Borderline Tuberculoid (BT) Hansen's disease.

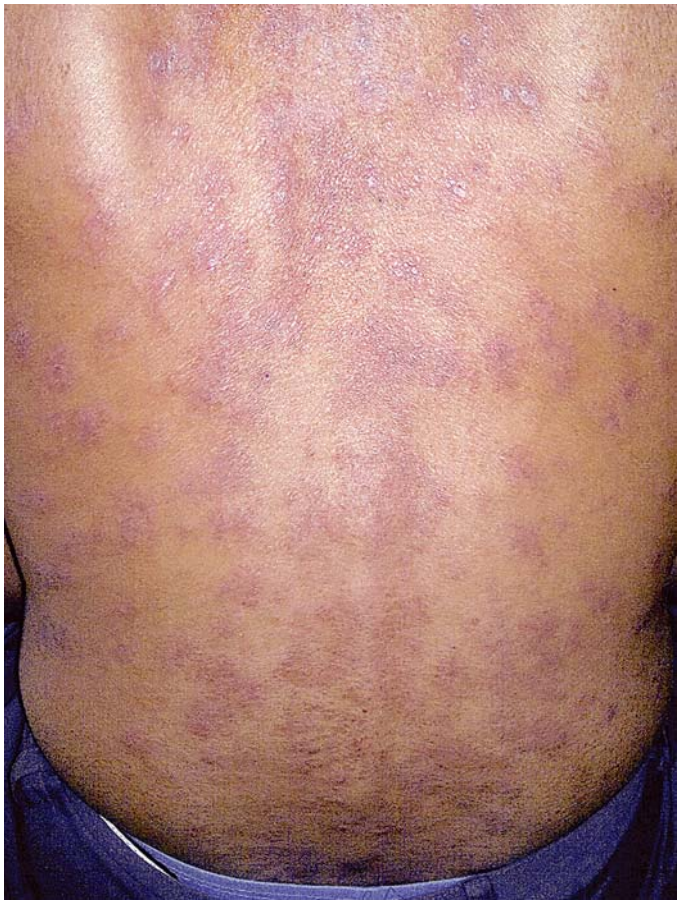

Fig. 31.4: Infiltrated plaques in drug reaction with eosinophilia and systemic symptoms (DRESS).

Marked erythema and edema of face with periorbital accentuation (25%–95% in various studies) is another hallmark of DRESS (Fig. 31.5).[7,16,20,21] Facial edema has been cited as a marker of internal organ involvement, but no such association was observed by us.[12,20] Facial erythema and edema are noted to be more conspicuous in phenytoin-induced DRESS.[20]

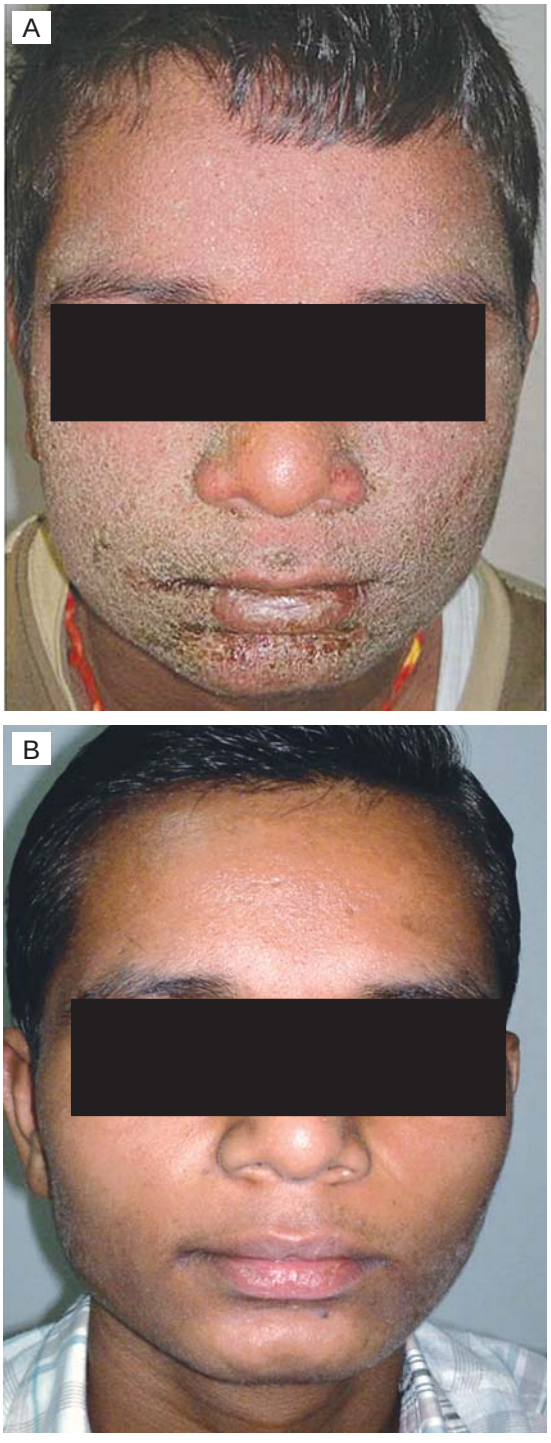

Fig. 31.5: (A) Marked erythema and edema of face in DRESS, caused due to carbamazepine; (B) The same patient 2 weeks after withdrawal of the offender and administration of systemic steroids.

Edema affecting distal extremities (mostly pedal edema) is also observed in many DRESS cases (Fig. 31.6).[7,19]

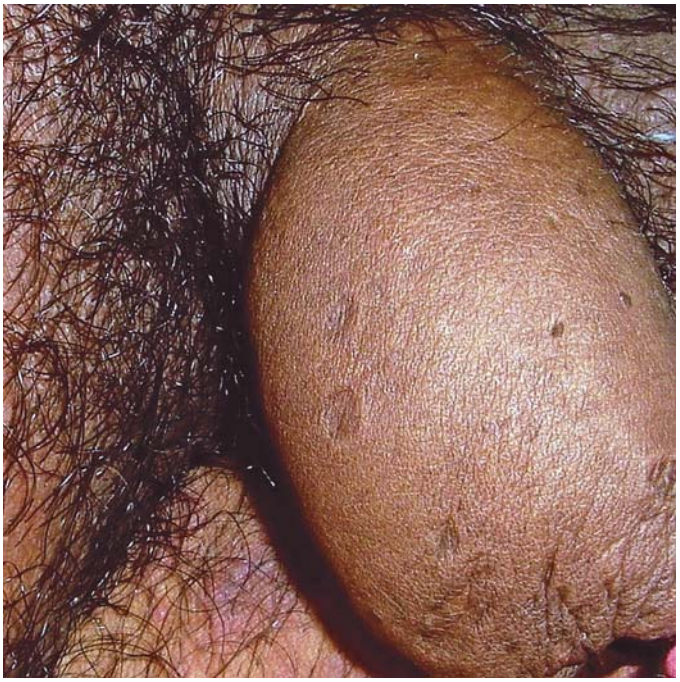

Fig. 31.6: Penile edema in drug reaction with eosinophilia and systemic symptoms (DRESS).

Other clinical types of cutaneous rash observed in DRESS are urticaria (Fig. 31.7), erythema multiforme (Fig. 31.8), purpuric rash (Fig. 31.9), pustular lesions (Fig. 31.10), SJS, and TEN.[7,12,14,16,18–21] We have reported a case of dapsone-induced DRESS where the diffuse erythrodermic rash progressed to fatal toxic epidermal necrolysis following sudden stoppage of systemic steroids by the patient herself.[20] Severity of cutaneous changes does not always reflect the severity of internal organ involvement.[12]

When a patient presents with pustular rash following drug intake, one needs to differentiate pustules of DRESS from that of acute generalized exanthematous pustulosis (AGEP). DRESS usually follows anticonvulsants, allopurinol, sulfonamides, and dapsone. Common drugs inducing AGEP are macrolides, quinolones, and aminopenicillins. But it is essential to remember that no clear cut difference exists between drugs producing these SCARS with more and more drugs being implicated as inducers of DRESS. A short latent period and diffuse erythema followed by appearance of disseminated nonfollicular pustules with a flexural predilection favor AGEP. Follicular pustules without any flexural accentuation indicate DRESS. In DRESS, pustules are mainly located on the face and upper thorax. Prompt response to drug withdrawal is observed in AGEP, whereas a prolonged disease course is noted in DRESS.[66]

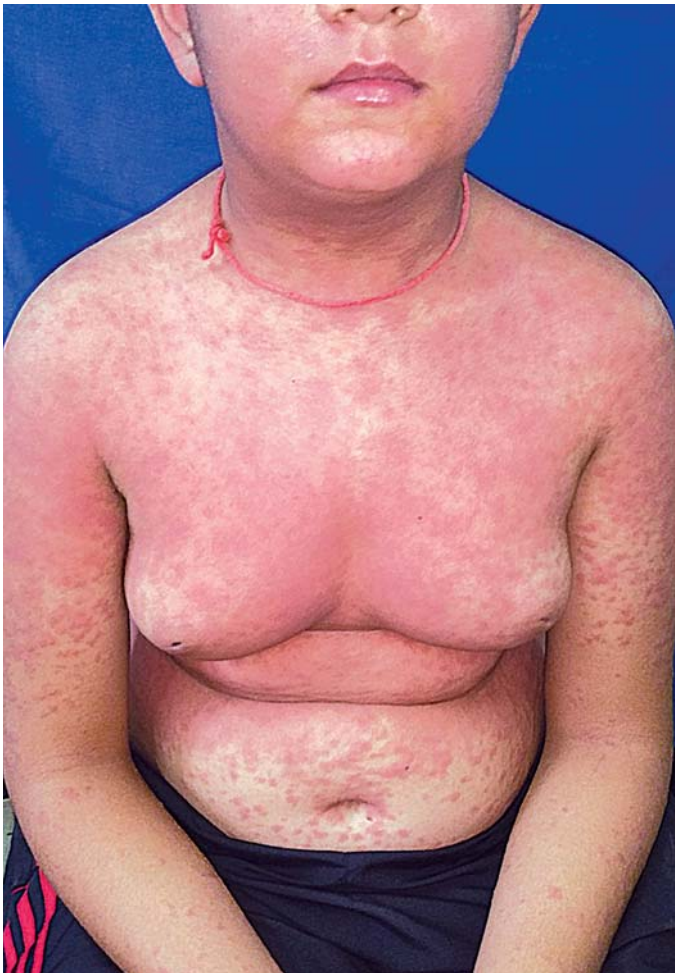

Fig. 31.7: Urticarial lesions in drug reaction with eosinophilia and systemic symptoms (DRESS).

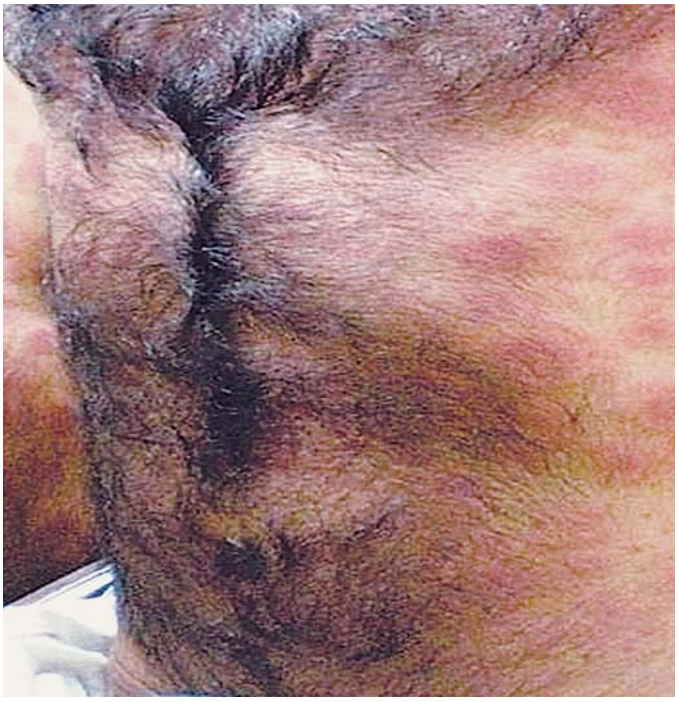

Fig. 31.8: Erythema multiforme like lesions in DRESS.

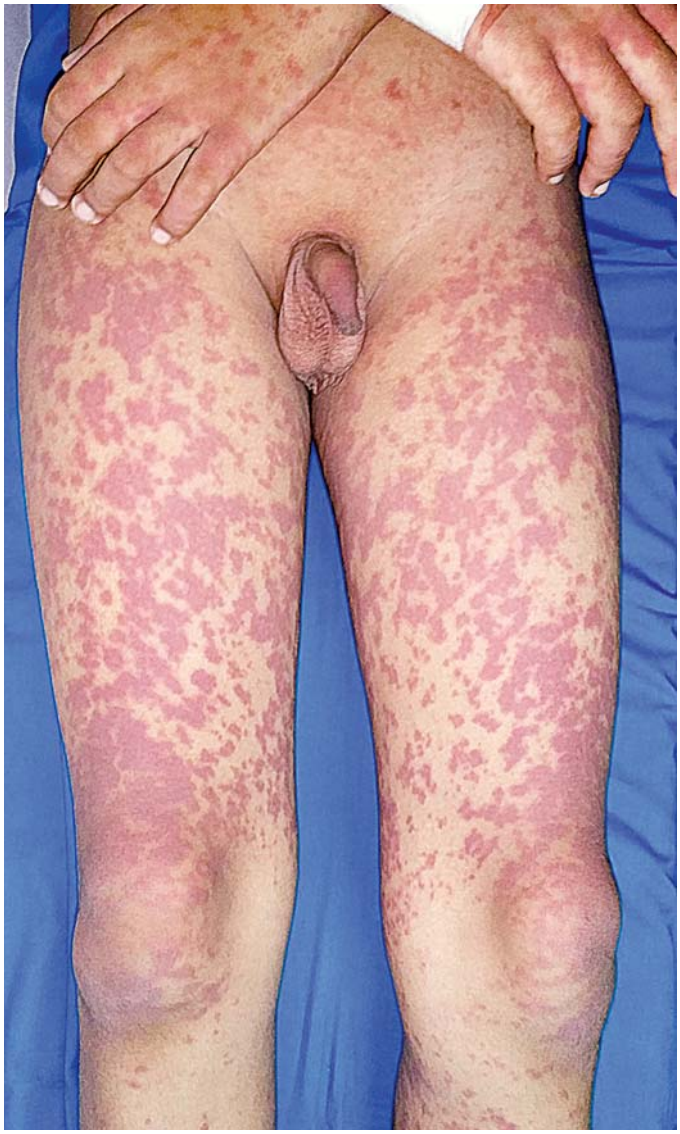

Fig. 31.9: Purpuric rash in drug reaction with eosinophilia and systemic symptoms (DRESS).

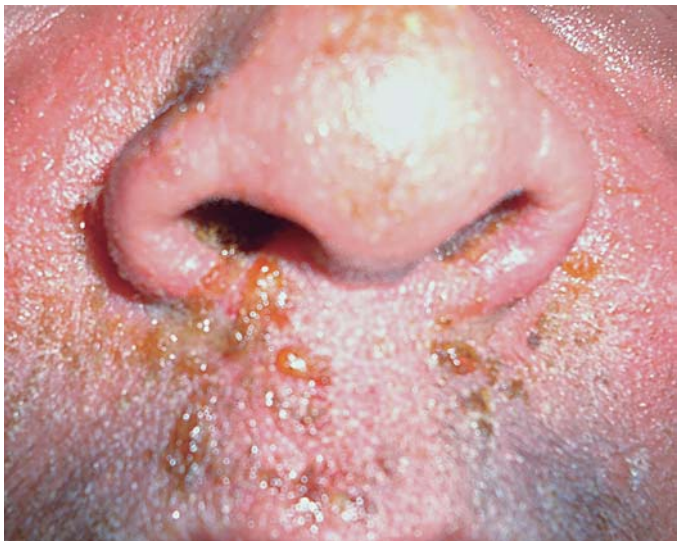

Fig. 31.10: Edema on face with 'vesiculo-pustules' and crusting in patient with DRESS.

Rash of DRESS often subsides with desquamation.[7,12,21] Rash suggestive of DRESS is defined as rash having 2/4 features—facial edema, infiltrated lesions, purpuric lesions on areas other than legs, and rash subsiding with psoriasiform desquamation.[25]

Mucosal Lesions

Incidence of mucosal lesions in DRESS ranges from 30% to 73% in various studies.[14,18,20,54–57] Involvement of mucosae is relatively mild in DRESS. Chelitis (Figs. 31.11 A and B) and pharyngeal erythema are frequently seen.[7,12,16,20] Conjunctival congestion and genital and oral ulcers are occasionally observed.[16,20] Strawberry tongue is a rare mucosal finding in DRESS, which when present, produce the diagnostic confusion of Kawasaki disease in children.[12] Dryness of mouth induced by edema and infiltration of salivary glands is another feature.[16]

Lymphadenopathy

Tender localized (especially cervical) or generalized lymphadenopathy (cervical, axillary, and inguinal) is a common finding in DRESS (18%–70%).[14,18,20,54–57]

Systemic Involvement

The most commonly affected internal organ is liver (50%–100%) and the most common abnormality is isolated elevation of liver transaminases.[7,14–16,18,20,21,54–57] Hyperbilirubinemia due to DRESS is a bad prognostic sign.[7] Hepatomegaly and splenomegaly can occur. On rare instances, hepatomegaly occur without any abnormality in the liver function tests.[12,15,16,21] It is stated that, in anticonvulsant-induced DRESS, the severity of hepatitis is related to the time interval between the onset of drug reaction and the withdrawal of the offender.[12,62] Renal involvement (10%–50% in different studies) varies from isolated proteinuria and hematuria to nephritis and renal failure.[7,12,14,18,20,54–57] Greater risk for renal involvement is seen in allopurinol-induced DRESS.[54,55] Myocarditis, a rare manifestation of DRESS, is usually associated with minocycline. Pneumonitis is associated with minocycline and abacavir.[7,14] Pancreatitis, meningitis and meningoencephalitis, spleen rupture, ulceration and gastrointestinal bleeding due to CMV and eosinophilic colitis, and esophagitis are the other less common systemic features documented in DRESS.[12,15,16,21,67] Visual impairment/visual loss due to uveitis is rarely described.[68,69] Systemic manifestations may be the presenting symptom or may be delayed up to several weeks after the onset of disease.[16,20]

Some patients manifest hypothyroidism following DRESS (autoimmune thyroiditis), which may resolve within the subsequent 12 to 18 months time.[7,12,16] Other autoimmune features described after DRESS are diabetes mellitus, systemic lupus erythematosus, alopecia areata, and sclerodermoid lesions.[7]

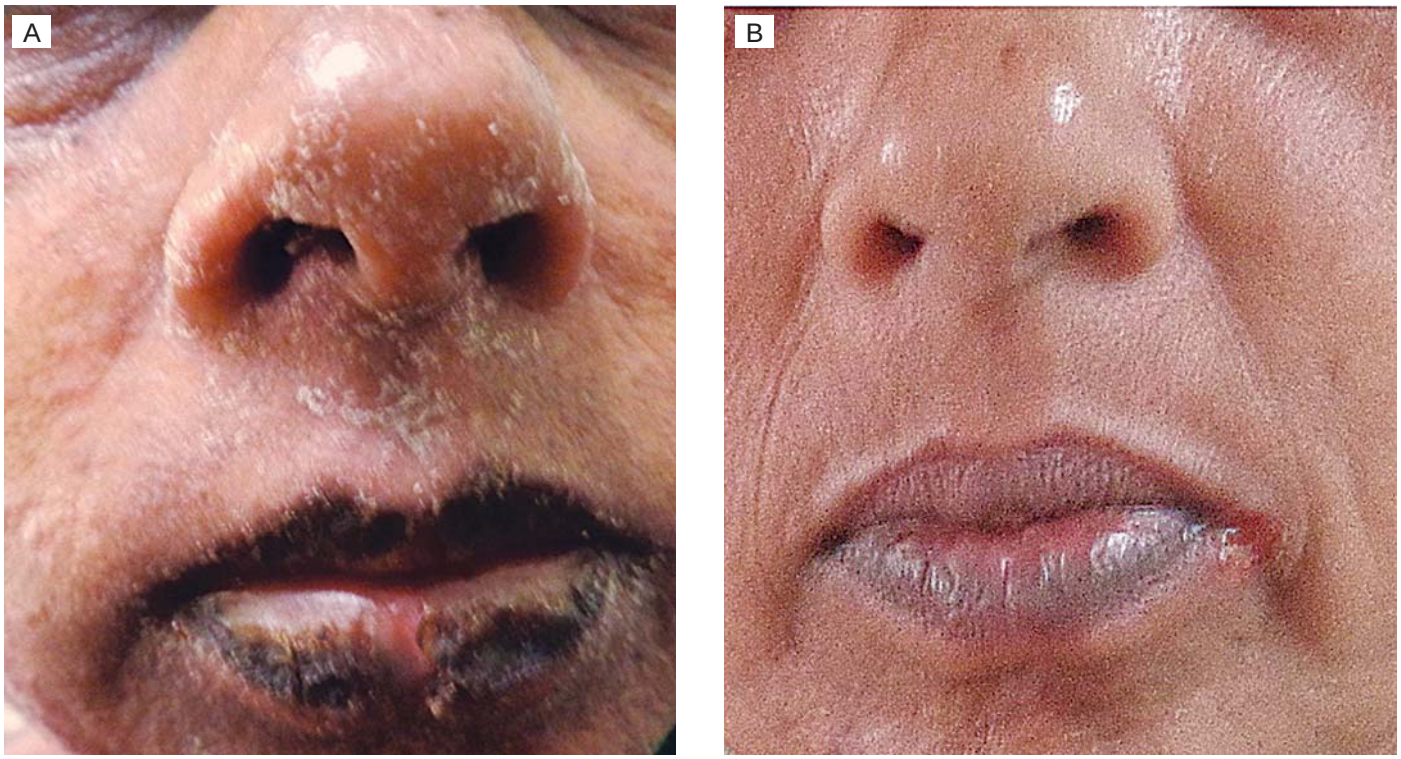

Fig. 31.11: (A) Hyperpigmentation, dryness, scaling, and crusting of lips—cheilitis, in DRESS; (B) Same patient at the time of discharge.

Hematological Features

Leukocytosis, lymphocytosis, eosinophilia (30%–90% in various studies), and atypical lymphocytes (7%–63% in different studies) in peripheral smear are commonly observed hematological findings.[7,12,15,16,21,54–57] Leukocytosis up to 50,000 leukocytes/mm^3 and eosinophil count above 20,000/mm^3 are reported.[10,16]

Eosinophilia may appear in the first week of DRESS or may be delayed to second or fourth week of disease.[16,20,70] Some studies suggest that more severe eosinophilia is indicative of serious DRESS, others including us found no such association.[12,20,55] An absolute eosinophil count greater than 1500 cells/mm^3 is said to be toxic to endothelial cells.[12]

It is documented that atypical lymphocytes in peripheral smear points to internal organ involvement.[20,71] Mononucleosis is noted in 40% of the affected.[72]

Though not very common, when present, leukopenia and thrombocytopenia are considered as bad prognostic signs.[7,54] Other less common hematological manifestations in DRESS are agranulocytosis and Coombs-negative and Coombs-positive hemolytic anemia. Erythrocyte sedimentation rate and complement levels are usually unaffected. Serum immunoglobulins fall in the beginning of DRESS.[12] Female sex, old age, drugs such as allopurinol, minocycline, and dapsone, delay in withdrawal of the offending drug, presence of atypical lymphocytes in peripheral smear, and evidence of reactivation of HHV-6 and CMV are considered as bad prognostic factors.[7,12,16,20,21,49,71]

The mortality rates documented in different studies vary from 0% to 40%.[7,18,20,54–57] It is higher in the elderly or in those with renal impairment or patients manifesting jaundice and hepatitis with reactivation of CMV.[16] The most common causes of death are hepatic failure followed by renal failure and myocarditis.[7,63]

Differential Diagnosis

DRESS being a diagnosis of exclusion needs to be differentiated from its several mimics (Box 31.3).[16,50,59–61,65,67] This is often very difficult in the absence of a definite diagnostic criteria or a confirmatory laboratory test. Unlike other drug reactions where a rapid response to withdrawal of the suspected drug (dechallenge) and administration of antihistamines or systemic steroids help the clinician to confirm the diagnosis, DRESS often shows a paradoxical flare-up on withdrawal of the offender, manifests newer and newer symptoms, or worsening of existing symptoms despite withdrawal of the offending drug.[7,16,21,67] Most often the clinician has to rely on history, rule out other probable differential diagnoses through reliable tests, and treat the patient under close monitoring so as to detect systemic complications as when they arise.

Box 31.3: Differential diagnoses of DRESS

- **Infections:** Infectious mononucleosis, viral hepatitis, measles, dengue fever, human immunodeficiency virus infection, leptospirosis, typhoid fever, rickettsial infection, septicemia, infective endocarditis
- **Inflammatory diseases:** Adult onset Still's disease, systemic lupus erythematosus, Kawasaki disease, viral reactivation with eosinophilia and systemic symptoms, idiopathic hypereosinophilic syndrome
- **Other drug reactions:** Maculopapular drug rash, SJS/TEN, AGEP
- **Malignancy:** Leukemia, lymphoma, paraneoplastic dermatoses

AGEP - acute generalized exanthematous pustulosis; SJS/TEN - Stevens-Johnson syndrome/toxic epidermal necrolysis.

Source: Chen et al.[7]; Kumari et al.[12]; Criado et al.[16]; Sasidharanpillai et al.[19]; Shiohara et al.[21]

Laboratory Investigations

Complete hemogram and renal and liver function tests will give an idea regarding the predominant inflammatory cells and the involvement of internal organs. Absolute eosinophil count and liver function test, if found within normal limits, should be repeated at frequent intervals since eosinophilia and hepatic involvement could be delayed up to second or fourth week of disease. Peripheral smear analysis for malarial parasites and atypical cells, ultrasound examination of abdomen and pelvis, electrocardiogram, blood culture, urine culture, and serology for HIV infection may help to rule out other probable diagnoses and to identify involvement of other systems in DRESS. Patients with respiratory symptoms should be advised chest radiography since pneumonitis and pleural effusion are observed in DRESS. All those showing altered liver function test should be tested for viral hepatitis. Antinuclear antibody profile and serology for infectious mononucleosis, leptospirosis, typhoid fever, rickettsia, dengue, and chikungunya infections should be carried out when in doubt. A better diagnostic test for EBV infection is detection of IgM antibodies to viral capsid antigen since monospot test and Paul Bunnel test can be negative in some cases of infectious mononucleosis, especially in children.[73] Echocardiogram will help the clinician to rule out infective endocarditis, a condition that

can present as persistent pyrexia or to detect DRESS induced myocarditis. Low platelet count, reduced erythrocyte sedimentation rate and elevated serum ferritin, lactate dehydrogenase, and triglyceride level in the setting of DRESS suggest hemophagocytosis and bone marrow analysis will help to confirm.[7,16,64] Thyroid function test and antimicrosomal thyroid antibody assay at the time of DRESS and then once in 2–3 months is advisable to detect DRESS-induced hypothyroidism.[12]

High lymphocyte count, high serum ferritin, and elevated serum creatinine at initial presentation are suggested as predictors of severe disease. High eosinophil count at initial presentation is said to be associated with prolonged clinical symptoms.[55,64,74,75]

Histopathology

No pathognomonic histology is identified for DRESS.[71,76] Rather than a diagnostic tool, biopsy helps to rule out other diagnoses in DRESS. The most common histological feature documented in DRESS is superficial perivascular inflammatory infiltrate mainly composed of lymphocytes (Fig. 31.12A).[71,76,77] Other frequently noted features are spongiosis, keratinocyte necrosis (Fig. 31.12B), and interface dermatitis (Fig. 31.12C). Epidermal changes noted include hyperkeratosis, parakeratosis, and dyskeratosis. Though peripheral blood eosinophilia is a common manifestation of DRESS, eosinophils in the dermal infiltrate are seen only occasionally (Fig. 31.12D).[71,76] Though not common, pseudolymphomatous histology (Fig. 31.12E) and leukocytoclastic vasculitis are observed in DRESS.[77,78] Interface dermatitis with or without apoptotic keratinocytes is said to be indicative of hepatic involvement in patients with erythema multiforme lesions.[77] But in a study conducted by us, this was observed in patients manifesting maculopapular rash, but not in those with erythroderma.[71] A dense dermal inflammatory infiltrate is suggested to be an indicator of systemic involvement and the presence of eosinophils in the inflammatory infiltrate predicts intense pruritus with recurrent flare-ups.[71] An important role for effector and regulatory $CD8^+$ T cells in the pathogenesis of DRESS has been suggested. CD8 +ve and granzyme B+ve lymphocytes are observed in DRESS with severe skin involvement.[21,80] Our impression after analysis of histopathology specimens of nine patients was that in the appropriate setting, varying combinations of epidermal hyperplasia, spongiosis, parakeratosis, and individual necrotic keratinocytes in the background of a lymphocyte predominant dermal infiltrate (with some atypia) favor the diagnosis of DRESS.[71]

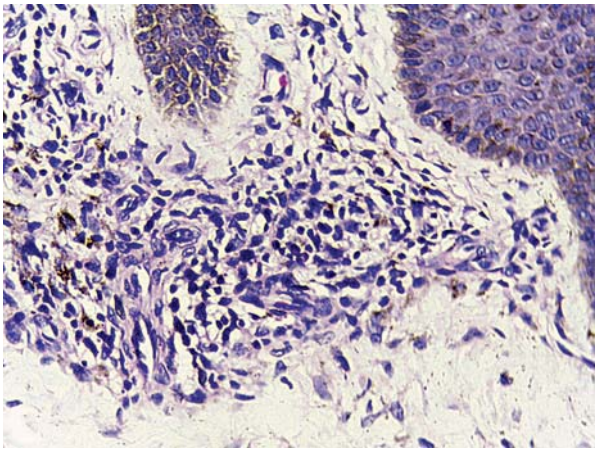

Fig. 31.12A: Skin biopsy from the lesion of DRESS showing perivascular inflammatory infiltrate composed of lymphocytes and occasional eosinophils (H&E, x400).

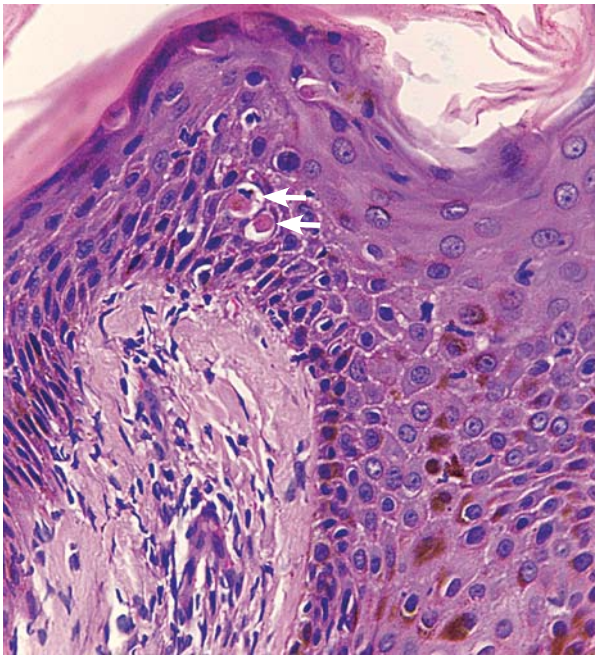

Fig. 31.12B: Skin biopsy from the lesion of DRESS showing apoptotic keratinocytes (H&E, x400).

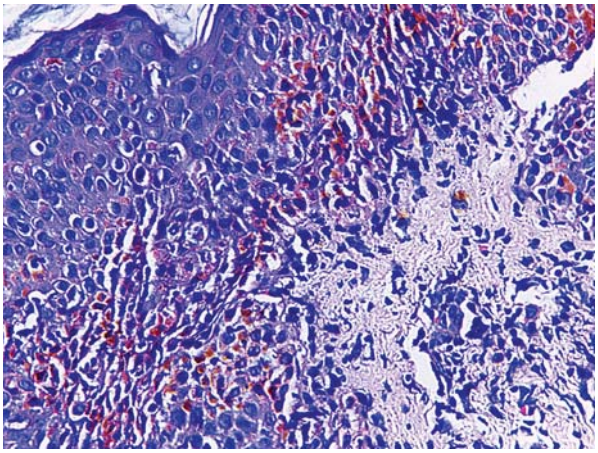

Fig. 31.12C: Skin biopsy from the lesion of DRESS showing basal cell degeneration and interface dermatitis (H&E, x400).

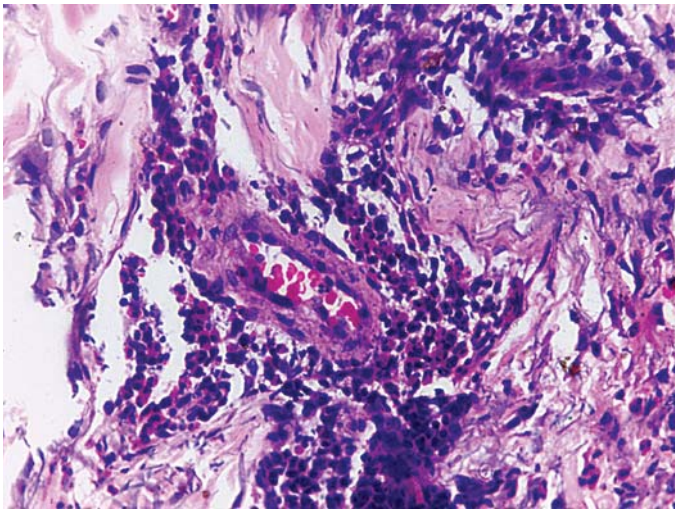

Fig. 31.12D: Skin biopsy from the lesion of DRESS, showing eosinophil rich perivascular inflammatory infiltrate (H&E, x400).

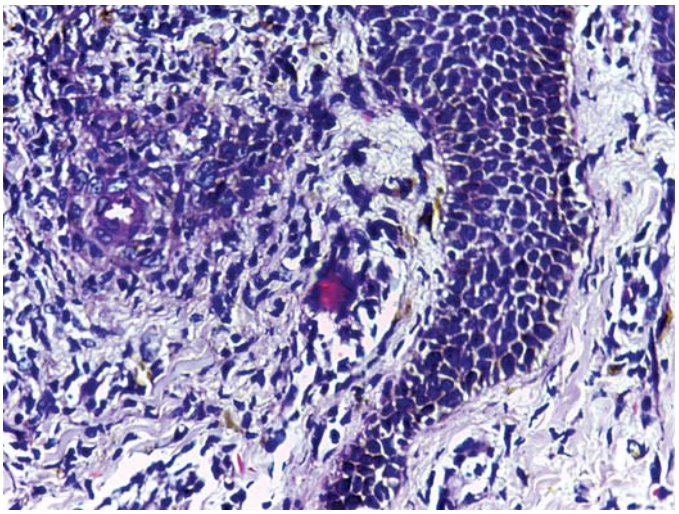

Fig. 31.12E: Skin biopsy showing atypical lymphocytes (H&E, x400).

To Determine the Reactivation of Herpes Viruses

Presence of HHV-6 DNA in cell-free specimens such as serum, plasma, or cerebrospinal fluid is more suggestive of an active viral replication, though this can occur intermittently in latent infection also. Viral DNA usually becomes undetectable with the appearance of antibodies in primary infection. Reverse transcriptase polymerase chain reaction (RT-PCR) in peripheral blood mononuclear cells is an ideal tool to diagnose active replication of HHV-6 and will yield a negative result in latent infections.[44] Detection of viral DNA, rising titers of anti HHV-6 IgG levels, and a constant level of IgM antibody point to HHV reactivation rather than primary infection.

In EBV infection, IgG and IgM antibodies to viral capsid antigen will be present at the onset of infection itself. Antibodies against nuclear antigen appear later. So EBV primary infection may be diagnosed in the presence of IgG and IgM viral capsid antibodies and negative IgG antibodies to nuclear antigen.[73] Detection of viral DNA and antibodies to EBV nuclear antigen along with antibodies to viral capsid antigen indicates reactivation.[73]

Though more commonly associated with herpes virus reactivation, DRESS has been rarely reported in the context of primary infection as well.[81]

Patch Test

A multicenter study on patch testing in SCAR documented positive patch test result in 64% of the 72 cases of DRESS tested. The same study suggested that patch testing may not be useful in allopurinol- and salazopyrine-induced DRESS. The current opinion is that patch test can aid in confirming the offender in DRESS induced by certain drugs including anticonvulsants and β-lactam antibiotics.[82]

Lymphocyte Transformation Test

It is reported that lymphocyte transformation test can confirm the suspected drug, if performed at the right time. Unlike other drug reactions (including SJS/TEN), where a positive response is obtained within the first week of rash, the ideal time to perform the test in DRESS is within 5–8 weeks of onset of rash. The negative response observed in early weeks of DRESS is attributed to the expansion of regulatory T cells in its initial stages. Another interesting finding noted is the persistence of positive response to lymphocyte transformation test for months to years after subsidence of DRESS whereas in all other drug reactions, this becomes negative within 5–8 weeks of onset of disease. There is no satisfactory explanation to the question that how the patient's lymphocytes remain active for long periods in DRESS, even when his/her system remains unexposed to the sensitizing drug. One postulate is that the herpes viruses that were reactivated during the course of DRESS could be keeping the lymphocytes in an activated state. Lymphocyte transformation test is a useful tool in DRESS when performed at the proper time.[83]

TREATMENT

No standard guide lines are available for the management of DRESS. The French Society of Dermatology has published a consensus on the management of DRESS/DIHS (Table 31.6).[84]

The greatest dilemma is when to suspect DRESS? On the day of presentation, we will not be able to make a diagnosis of DRESS since many of the features

Table 31.6: The French Society of Dermatology consensus guidelines on the management of DRESS/DIHS

DRESS without signs of severity	Potent or super potent topical steroids with emollients and antihistamines
DRESS with signs of severity (transaminases >5 times above normal, renal/cardiac involvement, pneumonia, hemophagocytosis)	Systemic steroids equivalent to 1 mg/kg/day of prednisone and multidisciplinary care
DRESS with life-threatening signs (Hemophagocytosis with bone marrow failure, encephalitis, severe hepatitis, renal failure, respiratory failure)	Systemic steroids with intravenous IgG at a dose of 2 g/kg over 5 days under multidisciplinary care. It is advised not to give immunoglobulin alone
DRESS with signs of severity and confirmed major viral reactivation	Systemic steroids and antivirals like ganciclovir and/or intravenous IgG

DRESS - drug reaction with eosinophilia and systemic symptoms; DIHS - drug-induced hypersensitivity syndrome.
Source: Descamps et al.[84]

develop over the subsequent days and each patient presents with his/her own constellation of symptoms and signs. So whether to start systemic steroids or to manage conservatively with withdrawal of the drug, emollients, and antihistamines as for a less severe drug reaction poses a major difficulty for the clinician. It would be beneficial to start systemic steroids after withdrawal of the offending drug, if a suspected case of drug reaction manifests any of the following: (1) Drug reaction following well-known inducers of SCAR, (2) rash involving >50% of body, (3) facial edema and/or erythema, (4) constitutional symptoms such as fever, (5) systemic involvement, (6) eosinophilia, and (7) presence of atypical cells in peripheral smear. The rate of steroid taper can be modified according to the diagnosis that evolves over the subsequent days.

Patients can be managed with 4–8 mg of parenteral dexamethasone in one or two divided doses per day, which can be changed to oral prednisolone at the time of discharge. Topical steroids, emollients, and first-generation antihistamines help in relieving the cutaneous symptoms.[7] If a coexisting infection cannot be ruled out, it is advisable to start antibiotics; but as far as possible limit the number of drugs to essential minimum. If possible avoid amoxicillin and penicillins, given their ability to activate herpes viruses.[46]

DRESS with systemic involvement requires multidisciplinary evaluation and care. Ursodeoxycholic acid and high-dose intravenous N-acetyl cysteine are tried in DRESS with hepatic involvement.[85–89] N-acetyl cysteine acts by replenishing cells with antioxidant capacity and by preventing cytokine-mediated immune reactions. Ursodeoxycholic acid is believed to have a beneficial effect in drug-induced cholestasis by replacing toxic hydrophobic bile acids with nontoxic hydrophilic bile acids. Moreover, ursodeoxycholic acid has cytoprotective, immunomodulatory, and antiapoptotic actions. But more data are needed to establish the efficacy of these drugs in DRESS/DHS.[89,90,91] Close monitoring in consultation with respective specialists is required in case of renal, lung, or cardiac involvement. Patients may require hemodialysis or supportive ventilatory care.

Many authors have warned against the rapid taper of steroids in DRESS.[7,12,16,21,67] On most occasions, flares precipitated by rapid steroid taper respond to increasing the steroid dose to the lowest previous dose that was able to control the reaction and attempting a slower taper.[19,20,67] Eshki et al. reported a patient who developed recurrent flare-ups necessitating treatment up to 1 year.[49]

Other treatment options recommended in steroid unresponsive DRESS are methyl prednisolone pulse therapy (30 mg/kg/day for 3 days), intravenous IgG (400 mg/kg/day for 5 days) and plasmapheresis or a combination of these.[16,49] Cyclosporine (100 mg twice daily for 5 days) and cyclophosphamide (750 mg/m^2 intravenously followed 2 weeks later by 100 mg orally daily for 6 months) are found to be useful, but needs more data on their efficacy.[62,68,69,92,93] Systemic steroids with ganciclovir are found beneficial in patients with viral reactivation.[84]

In aromatic anticonvulsant-induced DRESS, other aromatic anticonvulsants and lamotrigine should be avoided. It is preferable to avoid sodium valproate as well in the acute stage of aromatic anticonvulsant-induced DRESS/DHS owing to its hepatic metabolism.[12] Levetiracetam, clobazam, or benzodiazepines could be tried as replacement drugs.[12,37]

Patient Education

Patients should be warned of the possible disease flares and instructed to seek medical aid immediately

in case of disease flare. Educate the patients not to stop systemic steroids on their own without tapering. In case of DRESS by drugs such as anticonvulsants, allopurinol, and abacavir, it is better to avoid the same in first-degree relatives, if it is not possible to screen them for the presence of HLAs known to precipitate DRESS.

DRESS/DIHS remains a less known, unique, and unpredictable SCAR. More prospective studies in different population groups may clarify its several unknown aspects.

LEARNING ESSENTIALS

- The long interval between the onset of drug intake and the appearance of symptoms, variable clinical features, and the unpredictable disease progression makes DRESS/DHS a diagnostic challenge.
- It is of paramount importance to remember that the initial symptom in DRESS can be fever.
- DRESS/DHS should be an important differential diagnosis in all cases of pyrexia of unknown origin.
- Withdrawal of the offending drug and administration of systemic steroids which is tapered very slowly is the recommended treatment.
- Patient needs close evaluation in a tertiary care institution since multiorgan failure is not an infrequent complication of DRESS.
- The therapeutic options found useful in steroid resistant cases are intravenous IgG, cyclosporine, and cyclophosphamide.

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Chapter

32

Acute Generalized Exanthematous Pustulosis

Asit Mittal • Sharad Mehta

SUMMARY

Acute generalized exanthematous pustulosis (AGEP) is one of the severe cutaneous adverse reaction characterized clinically by rapid development of itchy, nonfollicular sterile pustules on an erythematous base. In contrast to the other serious adverse cutaneous drug reactions, mucous membrane involvement is absent or minimal. Drugs are the main cause of AGEP. Withdrawal of suspected drug is essential part of management and usually sufficient for the rash to settle. Sometimes, topical corticosteroids may also be needed. The use of systemic steroids and other immunomodulators in the management is controversial.

INTRODUCTION

Acute generalized exanthematous pustulosis (AGEP) is one of the severe cutaneous adverse reactions clubbed together with other serious drug rashes such as Stevens¬Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), generalized bullous fixed drug eruption (GBFDE), and drug reaction with eosinophilia and systemic symptoms (DRESS). It is characterized by the rapid development of itchy, nonfollicular sterile pustules on an erythematous base with no or minimal mucous membrane involvement. It is usually seen after drug intake and there is marked improvement within few days of removal of causative drug.

HISTORY

Baker and Ryan[1] in a description of a series of 104 cases of pustular psoriasis detected a subgroup of five patients who had no history of psoriasis and in whom the episode of pustular eruption was very acute, resolved quickly, and did not recur. They named this subgroup as *exanthematic pustular psoriasis.* Subsequently, many cases with similar clinical features were described under different names such as *toxic pustuloderma and pustular drug rash.* Beylot et al.[2] proposed the name "acute generalized exanthematous pustulosis" to describe the disease.

EPIDEMIOLOGY

AGEP can affect any age. Both genders are equally affected. In one study, association with HLAB51, DR11 and DQ3 was found to be more frequent than that in the average population.[3]

ETIOLOGY

Drugs are the most common cause of AGEP. A wide variety of drugs have been implicated in many case reports and large series (Table 32.1). Antibacterial drugs are the most frequent triggers. A high proportion of these cases have been attributed to aminopenicillins or macrolides. An increasing number of cases attributed to antimycotic drugs are also being reported. Interestingly, the spectrum of drugs that cause AGEP is different from that of SJS/TEN with pristinamycin, ampicillin/amoxicillin, quinolones, hydroxychloroquine, sulfonamides, terbinafine and diltiazem being associated with the highest risk and allopurinol showing relatively insignificant risk.[4–7]

The latent period between drug exposure and onset of the reaction is typically within 48 hours, at times as early as within 24 hours.[8] Besides drugs, this type of reaction pattern can occasionally be seen with infectious agents such as parvovirus B19,[8] Chlamydia pneumoniae,[9] and cytomegalovirus.[10] AGEP has also been reported after contact with mercury[11] and spider bites (brown recluse spider).[12]

Table 32.1: Drugs associated with AGEP

Drugs highly associated with AGEP	Less strong associations with AGEP	No significant association with AGEP
Pristinamycin	Corticosteroids	Acetaminophen
Aminopenicillins	Macrolides	Calcium channel blockers
Hydroxychloroquine	Oxicam NSAID	Thiazide diuretics
Sulfonamides	Antiepileptic drugs	Sartans
Quinolones		Allopurinol
Terbinafine		Cephalosporins
Diltiazem		Acetylsalicylic acid
		β-blockers
		ACE inhibitors
		Benzodiazepines

ACE - angiotensin-converting enzyme;
NSAID - nonsteroidal anti-inflammatory drug;
AGEP - acute generalized exanthematous pustulosis.

Source: Roujeau et al.[4]; Miteva et al.[5]; Vassallo et al.[6]; Di Lernia and Ricci.[7]

PATHOGENESIS

AGEP manifests 1–3 weeks after the drug intake. However, if the patient is already sensitized, the subsequent episode develops much earlier, within few hours to 2–3 days. The quick onset of skin symptoms and signs suggest an immunological recall mechanism. The presence of sterile pustules suggests recruitment of neutrophils to the site of action as an important event in AGEP.[13–19]

AGEP is believed to be a T-cell mediated disease. After exposure to drug the activated drug specific T-cell migrate to epidermis and dermis and these drug specific CD8 T cells induce apoptosis of keratinocytes in epidermis by perforin/granzyme and Fas ligand pathway. During the initial stage of AGEP, the vesicles are composed mainly of drug-specific CD4 T cells. These cells release increased amounts of CXCL8, a potent neutrophilic cytokine, leading to the chemotaxis of neutrophils into the vesicles, causing the transformation of vesicles into sterile pustules.[14]

AGEP shows a predominant Th1 type cytokine profile with increased interferon gamma (IFN-γ) and granulocyte/macrophage colony-stimulating factor (GM-CSF) production.[16] This leads to augmented neutrophil survivability that enhances formation of sterile pustules.[14]

In some patients with AGEP there are occasionally CXCL8 producing CD4 T cells that demonstrate a Th2 cytokine pattern with interleukin (IL)-4 and IL-5 production.[16] Increased IL-5, a potent stimulator of eosinophil growth and differentiation, may explain the eosinophilia seen in approximately 30% of AGEP cases. Th17 cells may also play a role in the development of AGEP, as Th17 cells release IL-17 and IL-22, which have synergistic effects on keratinocytes production of CXCL8.[19–22]

CLINICAL FEATURES

Clinically, AGEP is characterized by sudden appearance of numerous, small, sterile, nonfollicular pustules on an erythematous background (Fig. 32.1), following drug intake. Mucous membrane involvement is usually absent or mild and is usually confined to a single site, most often the lips or buccal mucosa.

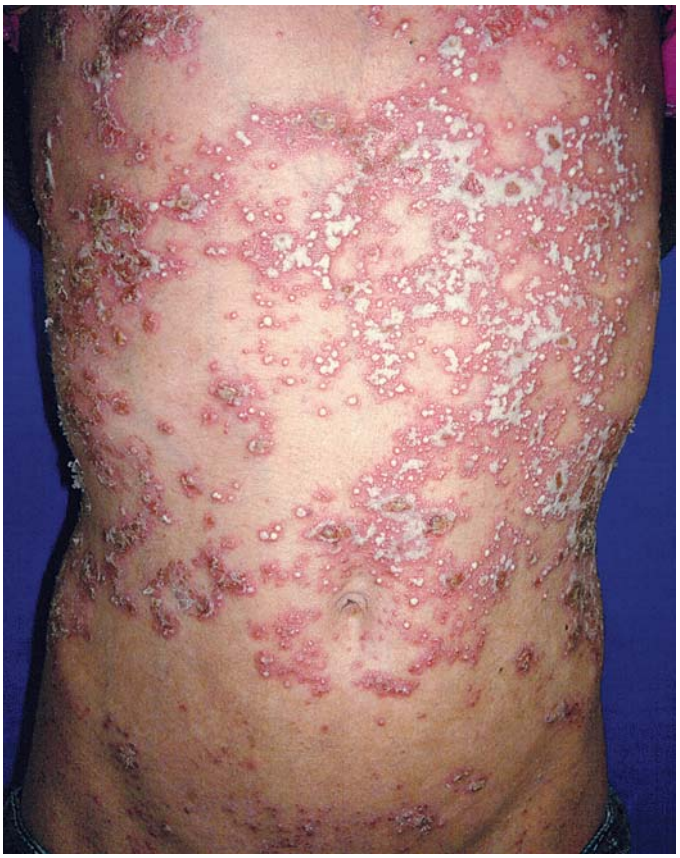

Fig. 32.1: AGEP over trunk induced by terbinafine. (Courtesy of Dr. K. Lekshmi Priya, Guwahati.)

The distribution favors the trunk (Fig. 32.2), flexures (Fig. 32.3) and intertriginous regions (Fig. 32.4). A variable degree of pruritus is present and patients are usually febrile. The disease resolves rapidly, within a few days, leaving behind postinflammatory desquamation (Fig. 32.5).

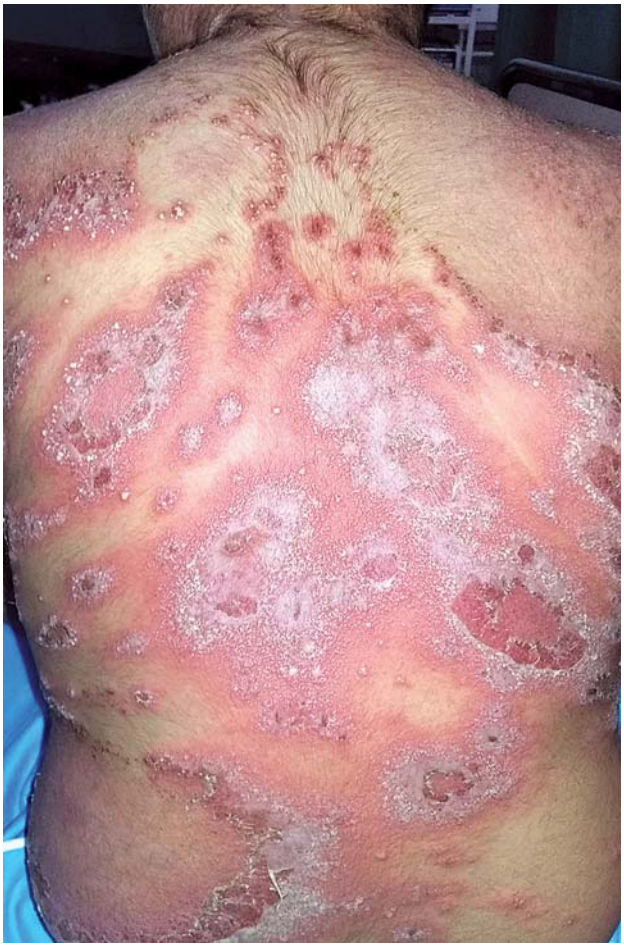

Fig. 32.2: AGEP showing numerous pustules and lakes of pus on back, induced by amoxicillin/clavulanic acid. (Courtesy of Dr. K. Lekshmi Priya, Guwahati.)

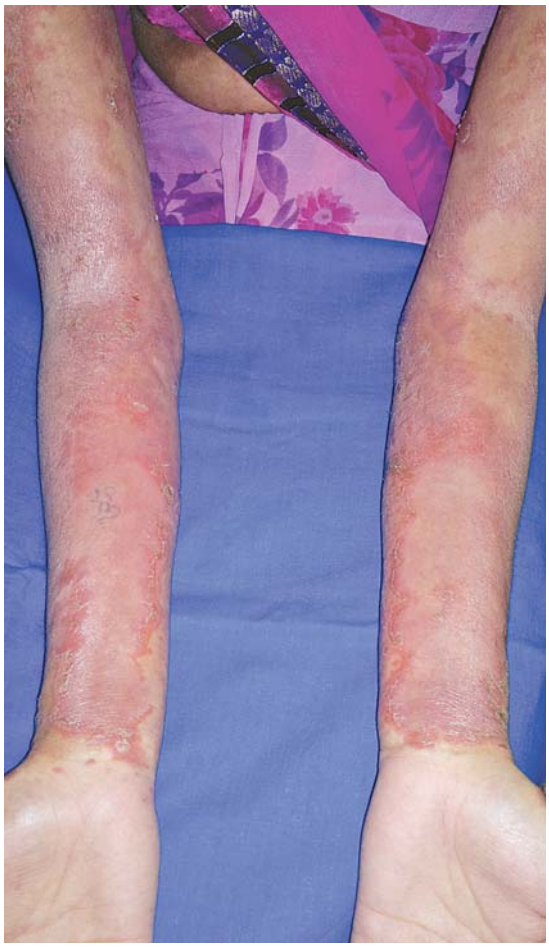

Fig. 32.3: AGEP over flexures of forearm, due to ciprofloxacin. (Courtesy of Dr. K. Lekshmi Priya, Guwahati.)

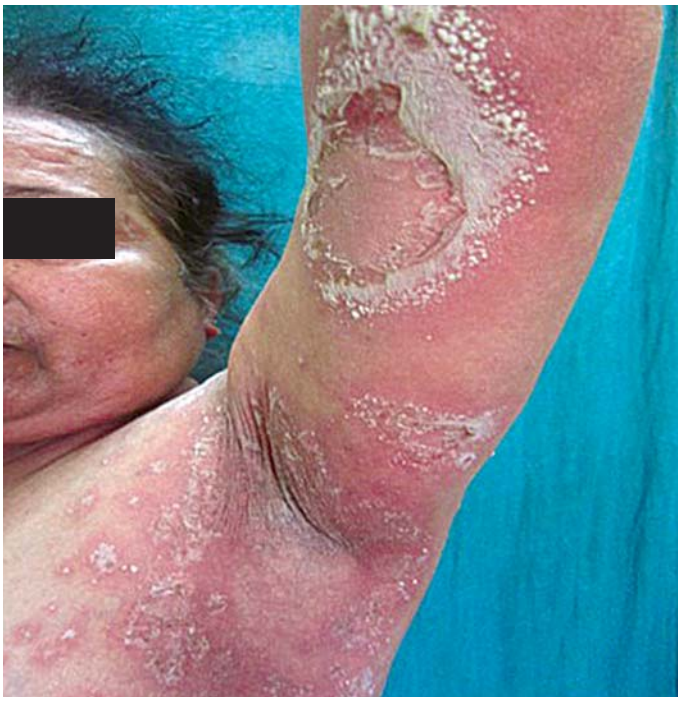

Fig. 32.4: AGEP induced by phenytoin over intertriginous areas. (Courtesy of Dr. Bela Shah, Ahmedabad.)

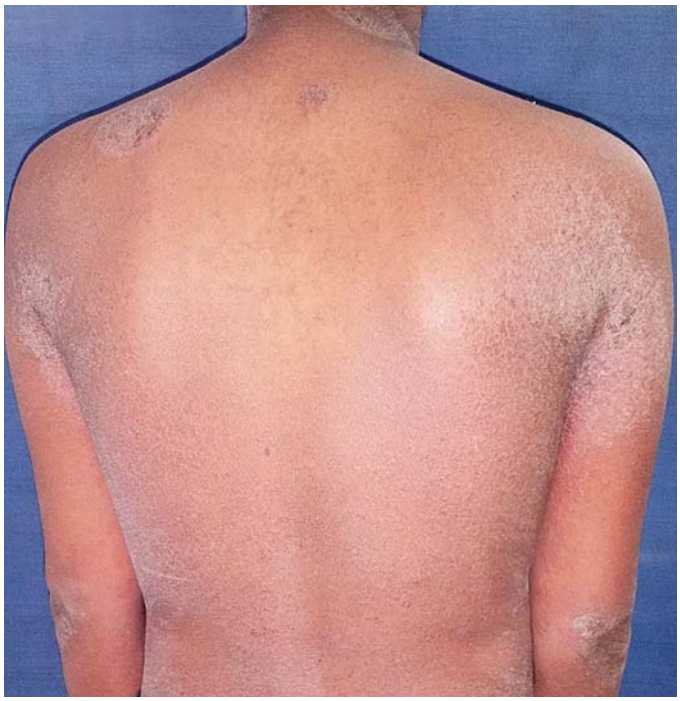

Fig. 32.5: Subsiding AGEP showing desquamation.

Although involvement of internal organ is uncommon in AGEP, hepatic, renal, and pulmonary dysfunction have been reported in patients with systemic involvement.[23] Hepatic involvement includes mild elevation of liver enzymes in either cholestatic or hepatocellular pattern. Renal involvement is seen in the form of slight reduction in creatinine clearance. Pulmonary involvement is characterized by bilateral pleural effusion.

INVESTIGATIONS

Leukocytosis with an elevated neutrophil count (7.5×10^9/L) is seen in almost all cases of AGEP.[23] Mild eosinophilia may be present in about one-third of patients. A slight elevation of aminotransferases and reduction in creatinine clearance can occasionally be seen. Elevated absolute neutrophil count and C-reactive protein levels can predict systemic organ involvement.

Hypocalcemia may be noted in severe cases as a part of complication.

HISTOPATHOLOGY

Histologic features of AGEP are characterized by intracorneal, subcorneal (Figs. 32.6 A and B), and/or intraepidermal pustules along with variable degree of spongiosis, exocytosis of neutrophils, and necrotic keratinocytes. Edema with neutrophilic and eosinophilic infiltrates is seen in dermis.[24-25]

The histologic features of plaque-type psoriasis, such as increased mitotic figures and tortuous, dilated blood vessels, are infrequently seen in AGEP.

DIAGNOSIS

The diagnosis of AGEP is often clinical as suggested by acute onset of rash after drug intake and typical distribution. A meticulous history is very important. Roujeau et al.[4] proposed a set of diagnostic criteria for AGEP that included:

1. Appearance of hundreds of sterile non-follicular pustules at flexural sites
2. Histopathological changes of spongiosis and epidermal pustule formation
3. Fever >38°C
4. Blood neutrophil count >7 × 10^9/L
5. Acute evolution with spontaneous resolution of pustules in less than 15 days

A newer set of diagnostic criteria developed by EuroSCAR group[26] is a standardized scheme based on the morphology (pustules, erythema, distribution, postpustular desquamation), clinical course [mucosal involvement, acute onset (10 days), resolution (15 days)], fever ≥38°C, polymorphonuclear leukocytes (PMN) ≥7000/mm^3), and histology. Based on these, the patients are classified as having definite, probable, possible, or no AGEP. The score is categorized as definite (8–12), probable (5–7), possible (1–4), or no AGEP (≤0).

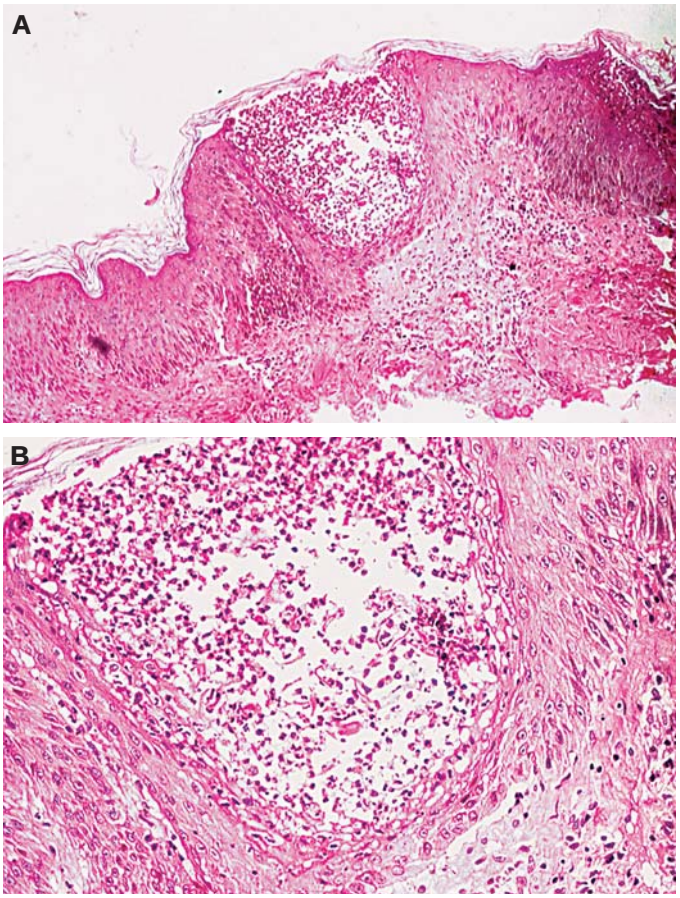

Fig. 32.6: (A) H&E (10x) AGEP histology showing intraepidermal subcorneal pustule containing neutrophils and eosinophils with dermal edema; (B) A higher magnification (H&E, 40x) of the same patient. (Courtesy of Dr. K. Lekshmi Priya, Guwahati.)

Drug Patch Testing

Drug patch testing (DPT) aids in diagnosis of AGEP and the most frequent results were observed with β-lactam antibiotics (mainly amoxicillin), pristinamycin, radiocontrast media. The results of the tests are positive within 6 hours. In patients with the history of AGEP, these patch test sites may show CD4 and CD8 T cells specific to the inciting drug.[13,27]

DIFFERENTIAL DIAGNOSIS

A wide spectrum of cutaneous diseases (Table 32.2) or reactions can cause pustular eruptions. Most of them can easily be differentiated from AGEP.

There still remains a group of diseases where differentiation from AGEP may be difficult, both clinically and histologically. These include:

Pustular Psoriasis (Von Zumbusch Type)

Morphology of the pustules is often indistinguishable in both pustular psoriasis of Von Zumbusch and AGEP (Fig. 32.3). Many authors have addressed this issue and until now no clear-cut guidelines for the differentiation of both entities exist. Table 32.3 lists a few differentiating features between AGEP and pustular psoriasis.

Subcorneal Pustular Dermatosis (Sneddon–Wilkinson Disease)

Sneddon–Wilkinson disease is characterized by larger, flaccid blisters with hypopyon formation, often arranged in a circinate pattern. In addition, evolution of the disease is far less acute. Lesions appear in crops over months or years, which is quite in contrast to AGEP.

Pustular Vasculitis

Bullous and/or pustular lesions may arise in lesions of leukocytoclastic vasculitis. In addition, there seems to be a special variant of leukocytoclastic vasculitis, which is characterized by the development of many small pustules which as opposed to AGEP are localized mainly on the dorsum of the hands and which might also be drug-induced. A marked leukocytoclastic vasculitis can be detected on histopathology.

Drug Hypersensitivity Syndrome

Drug hypersensitivity syndrome (DHS), also referred to as DRESS (an acronym for drug reaction with eosinophilia and systemic symptoms) may also show papulovesicles and/or papulopustules, the pustular component being usually less pronounced than in AGEP. In addition, patients show fever, lymphadenopathy, eosinophilia, often severe visceral involvement such as hepatitis, nephritis, pneumonitis, and/ or myocarditis.

Toxic Epidermal Necrolysis

The presence of "atypical" target lesions and the confluence of pustules mimicking a positive Nikolsky's sign may suggest the diagnosis of TEN in severe cases of AGEP.

Epidermal detachment in AGEP is much more superficial, and mucous membrane involvement is much more pronounced in TEN. Although differentiation in some cases might be difficult on clinical grounds alone, histology is significantly

Table 32.2: Differential diagnosis of AGEP

Bacterial folliculitis	Sweet's syndrome	Behcet's disease
Furunculosis	Impetigo	Staphylococcal scalded skin syndrome
Acneiform pustules	Impetiginized eczema	Varicella
Localized pustular contact dermatitis	Bowel bypass syndrome	Pemphigus foliaceus
Dermatophyte infections	Infantile chronic acropustulosis	Kaposi's varicelliform eruption
Pyoderma vegetans	Migratory necrolytic eruption of glucagonoma	

Table 32.3: Differentiation between AGEP and pustular psoriasis

	AGEP	Pustular psoriasis
History of psoriasis	Possible	Mostly
Distribution pattern	Predominance in the folds	More generalized
Duration of pustules	Shorter	Longer
Duration of fever	Shorter	Longer
History of drug reaction	Usual	Uncommon
Recent drug administration	Very frequent	Less frequent
Arthritis	Rare	30%

AGEP - acute generalized exanthematous pustulosis.

Source: Sidoroff et al.[26]

different in TEN, typically showing full thickness epidermal necrosis and only a very sparse inflammatory infiltrate.

TREATMENT

No specific treatment is recommended for AGEP except for withdrawal of the suspected drug and supportive care. Removal of the causative drug leads to improvement in symptoms within several days.[28] Moist dressings and antiseptic solutions are appropriate during the pustular phase to prevent infection. Antibiotics should be avoided, unless superinfection of the pustules occurs. Topical corticosteroids may be used for treatment of pruritus and inflammation in prolonged cases.[28] Emollient should be prescribed and continued throughout the phase of postpustular desquamation, until full skin integrity is restored. Systemic corticosteroids have also been used; however, evidence that systemic corticosteroids reduce disease duration is unclear.[29–31]

Multiple organ dysfunction in AGEP may occasionally require treatment in an intensive care unit.

PROGNOSIS

Although AGEP is classified as a severe drug rash, the internal organ involvement is less common than in other severe cutaneous drug reactions such as SJS/TEN and DHS and thus the prognosis is much more favorable. Withdrawal of the suspected drug alone causes remission in most of the cases without any long term consequences. Mortality is less than 5% and is as a result of multi-organ dysfunction and disseminated intravascular coagulation. Patients with comorbidities and severe mucosal involvement are at a higher risk of death.[32]

LEARNING ESSENTIALS

- AGEP is an acute severe cutaneous reaction pattern predominantly caused by drugs.
- Most common implicated drugs are aminopenicillin, sulfonamides, terbinafine, and hydroxychloroquine.
- It presents with fever and sudden appearance of generalized, nonfollicular pustules within 24–48 hours of intake of drug.
- Although clubbed together with other severe cutaneous drug rashes such as TEN, SJS and DRESS, it carries a relatively favorable prognosis.
- In most cases, withdrawal of drug is sufficient for remission of AGEP; however, use of topical and systemic steroid may help in quicker resolution of rash.

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Chapter

33

Cutaneous Adverse Drug Reactions to Anti-Infective Agents

Biju Vasudevan • Ankan Gupta

SUMMARY

Anti-infectives are one of the most common drugs causing cutaneous adverse drug reactions (CADRs) along with nonsteroidal anti-inflammatory drugs (NSAIDs). Immediate hypersensitivity reactions are common with this group especially antibacterials. As a group, they can cause any variant of cutaneous adverse drug reaction (CADR). The propensity to cause Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is highest with sulfonamides, which as a group is also notorious for having the highest risk for CADRs. Cross-reactions are very common with these group of drugs.

INTRODUCTION

Every drug has a potential to cause an adverse effect. CADRs manifest with myriad presentations, ranging from a trivial generalized pruritus to a maculopapular exanthem to toxic epidermal necrolysis (TEN). CADRs are often accompanied with fever and are identified by the treating physician as a case of *"fever with rash"* which gives rise to two significant questions in his mind:

1. Is this rash a part of the exanthematous fever or is it a reaction to the drug taken?
2. Should I treat it conservatively or should I prescribe anti-infectives?

Unfortunately for the dermatologists, it is often after embracing the latter option that the patient presents. To make things worse in our country, most of the drugs are accessible directly without prescriptions and alternative forms of medicines also exist which sometimes include medicines given wrapped in a piece of paper. Thus, regardless of the most probable offender drug, an anti-infective (which mostly is an antibiotic) is a part of the battery of drugs patient has consumed in the relevant admissible period. Hence, a thorough knowledge of the pharmacodynamics of anti-infectives and a detailed meticulous inquiry into the chronology of events go a long way in managing CADR.

Anti-infectives are drugs that can either kill an infectious agent or inhibit it from spreading. They include the following:

- Antibacterials
- Antifungals
- Antivirals
- Antiprotozoals

Drug reactions to antiretroviral drugs has been discussed in chapter 43. The commonly used anti-infectives and the various CADRs they produce are discussed in detail in the following sections.

ANTIBACTERIALS

In 2010, India was the world's largest consumer of antibiotics for human health at 12.9×10^9 units (10.7 units per person). The next largest consumers were China at 10.0×10^9 units (7.5 units per person), and the United States at 6.8×10^9 units (22.0 units per person).[1] Over-the-counter, nonprescription sales of antibacterials in India are among the highest in the world and sales of quinolones have increased in the last decade outnumbering macrolides and sulfonamides to sit third after cephalosporins and broad-spectrum penicillins.[2]

Adverse drug reactions common to all broad-spectrum antibiotics include opportunistic candidal infections, antibiotic-associated colitis, and gram-negative folliculitis.[3] Superficial thrombophlebitis observed after intravenous injection is seen with

most antibiotics, more distressing in some such as dicloxacillin and vancomycin. These adverse effects will not be discussed again in this chapter.

Penicillins

Group side effects: Hypersensitivity reactions such as maculopapular exanthem, urticaria, serum sickness are more common and serious with the intravenous therapy, although they have also been reported with oral therapy. An initial sensitizing exposure is usually required to stimulate the production of antigen-specific IgE and the clinical manifestations of hypersensitivity reaction are then seen on further exposures. Various "hidden" environmental/occupational exposures to the penicillins like in utero exposures, breast milk exposure, and occupational exposures can also act as triggers.

Penicillin G is the naturally produced penicillin. Over the years, many semi-synthetic penicillins have been developed and all forms of penicillins can cause drug-induced hypersensitivity reactions[4] and anaphylaxis,[5] making it imperative for every patient to have an intradermal test with penicillins.

Approximately, 10% of all patients report history of penicillin allergy, although in up to 90% of these cases, penicillin is finally tolerated.[5] Penicillins cross-react among themselves as well as with other β-lactams including cephalosporins (1%–5%) and carbapenems.[6]

Penicillins and cephalosporins have been associated with a peculiar exanthematous rash resembling the red gluteal area of baboons, which occurs after systemic exposure to contact allergens also. When limited to the buttocks, it is known as Baboon syndrome; however, when other flexures are involved, symmetrical drug-related intertriginous and flexural exanthem (SDRIFE) is a more appropriate terminology.[7]

Contact dermatitis has also been reported in people preparing penicillin solutions.[8]

CADR specific to important penicillins have been listed in Table 33.1.

Table 33.1: CADR to penicillins

Generic name	CADR
Penicillin G	Jarisch–Herxheimer reaction mainly in syphilis. Jarisch–Herxheimer reaction can manifest as exacerbation of skin lesions. This reaction can also be seen in borreliosis, leptospirosis, bartonellosis, and brucellosis. Erythroderma
Penicillin V	Black hairy tongue
Dicloxacillin	Shore nails, onychomadesis[9]
Amoxicillin	AGEP, SDRIFE, amoxicillin rash. In 3%–10% of children taking amoxicillin/ampicillin, a maculopapular or morbilliform rash (Fig. 33.1), known as the "amoxicillin rash" occurs after 72 hours of beginning medication. It starts on the trunk and later spreads. The rash is unlikely to be a true allergic reaction, and is not a contraindication for future drug usage. Rare: Angioedema, bullous pemphigoid, DRESS, EM, SJS/TEN, FDE, oral ulcers, xerostomia, LAD, Jarisch–Herxheimer reaction, petechial rash, pustuloderma
Ampicillin	Maculopapular pruritic rash within 7–10 days. Incidence of CADR due to ampicillin is quite high in patients suffering from infectious mononucleosis, cytomegalovirus, or acute lymphocytic leukemia (60%–100%) or when co-administered with allopurinol.[10] This increased hypersensitivity to ampicillin in presence of viral infection is a transient phenomenon and does not occur if ampicillin is used later for any other indication. AGEP, Baboon syndrome, anaphylaxis, autoimmune bullous dermatoses, erythema annulare centrifugum, FDE, SJS, and TEN. Black tongue (Fig 33.2) and glossitis have also been reported.
Piperacillin	Purpura/ecchymosis[11]
Amoxicillin-clavulanate	SJS/TEN (Fig. 33.3)
Piperacillin-tazobactam	SJS/TEN, DRESS, AGEP

CADR - cutaneous adverse drug reaction; AGEP - acute generalized exanthematous pustulosis; SDRIFE - symmetrical drug-related intertriginous and flexural exanthem; FDE - fixed drug eruptions; EM - erythema multiforme; DRESS - drug reaction with eosinophilia and systemic symptoms; SJS/TEN - Stevens–Johnson syndrome/toxic epidermal necrolysis; LAD - linear IgA Disease.

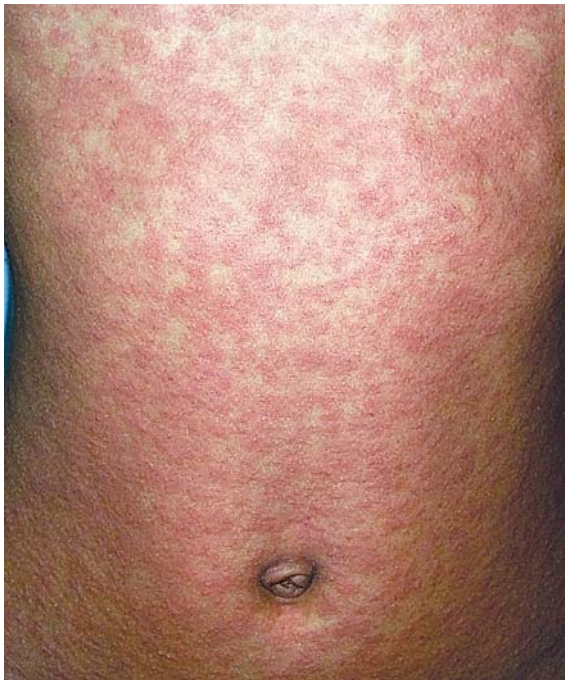

Fig. 33.1: Maculopapular rash in a patient on amoxicillin.

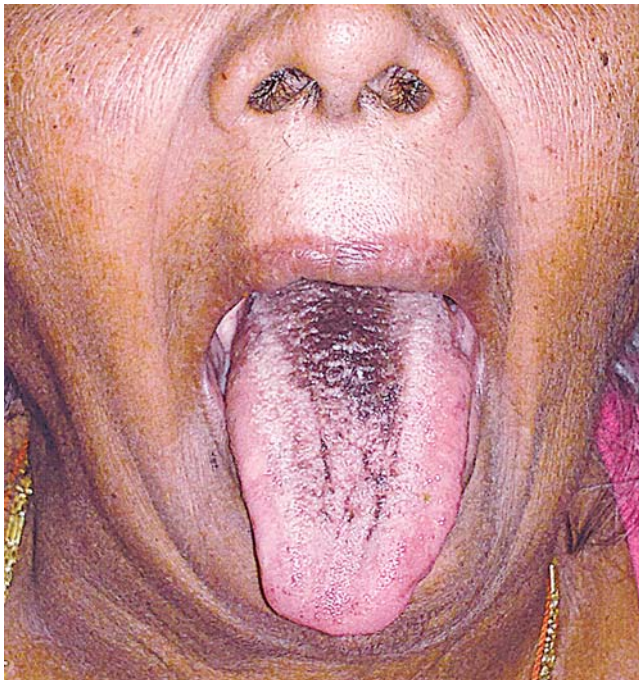

Fig. 33.2: Black hairy tongue in a patient on ampicillin.

Fig. 33.3: TEN in a child on amoxicillin-clavulanate.

Cephalosporins

Cephalosporins are also β-lactam antibiotics, which differ from penicillin by the substitution of its five-membered thiazolidine ring with a six-membered dihydrothiazine ring. Hypersensitivity reactions constitute the major CADR observed with cephalosporins.[12]

Risk of cross-reactivity in penicillin allergic patients is present but serious adverse events are seen in meagre 0.001%.[13] For carbapenems, cross-reactivity between β-lactam ring and penicillin restricts its use. Monobactams though can be safely given to patients with penicillin allergy.[14]

Since 1980s, the rate of cross-reaction between second- or third-generation cephalosporins and penicillin is found to be ≤5%. The degree of cross-reactivity is more for first-generation cephalosporins, however, a penicillin skin testing before initiating the cephalosporin therapy is advocated for all generations. Patients with history of penicillin allergy but whose skin tests are negative can receive cephalosporins safely.

CADR specific to important cephalosporins have been listed in Table 33.2.

Table 33.2: CADR to cephalosporins

Generic name	CADR
Cefuroxime	Jarisch–Herxheimer reaction,[15] Baboon syndrome
Cefaclor, cefprozil	Serum-sickness-like reaction, morbilliform rash, AGEP (Fig. 33.4)
Cefadroxil, cephalexin	Baboon syndrome (Fig 33.5), DRESS syndrome
Ceftriaxone	Rarely FDE

CADR - cutaneous adverse drug reaction; AGEP - acute generalized exanthematous pustulosis; DRESS - drug reaction with eosinophilia and systemic symptoms; FDE - fixed drug eruptions.

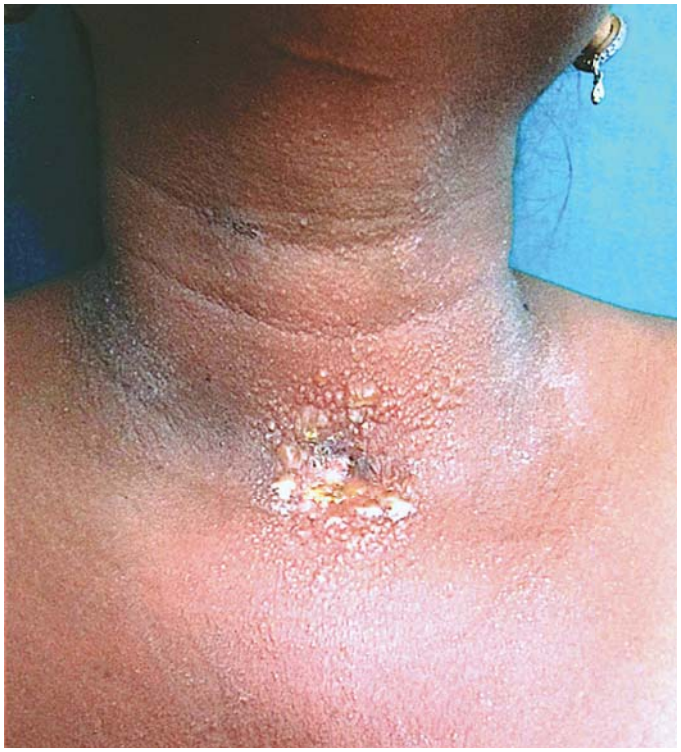

Fig. 33.4: AGEP in a female patient on Cefaclor. (Courtesy of Dr. Bela Shah, Ahmedabad.)

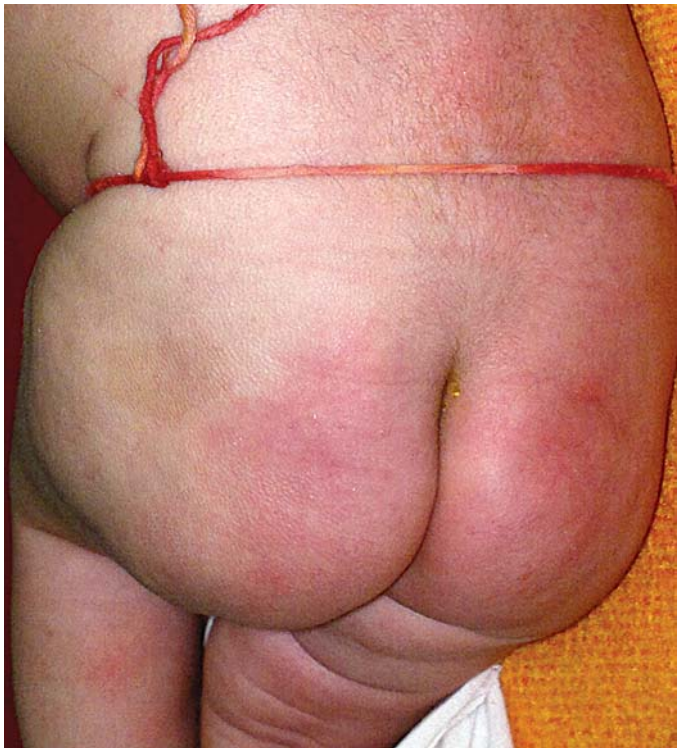

Fig. 33.5: Baboon syndrome to cephalosporin in an infant.

Other β-Lactams

Hypersensitivity and cross-reactivity are common to all such as penicillins and cephalosporins.

CADR specific to other β-lactams have been listed in Table 33.3.

Table 33.3: CADR to β-lactams other than cephalosporins

Generic name	CADR
Ertapenem, meropenem	AGEP, generalized rash, edema. Two cases of wound complications have also been seen
Aztreonam	EM, TEN, exfoliative dermatitis.[16]

AGEP - acute generalized exanthematous pustulosis; CADR - cutaneous adverse drug reaction; EM - erythema multiforme; TEN - toxic epidermal necrolysis.

Glycopeptides

Group includes vancomycin, telavancin, dalbavancin, and oritavancin.

Vancomycin: CADR includes the characteristic red man syndrome. Red man syndrome is characterized by increased warmth, flushing, pruritus, hypotension, pain, muscle spasms on the back and chest, dyspnea, and severe cardiovascular toxicity. More than 50% patients may experience the red man syndrome which is due to non-IgE-mediated histamine release after rapid infusion. This can be prevented by giving the infusion slowly and premedicating with antihistamines.

Other CADR specific to glycopeptides have been listed in Table 33.4.

Table 33.4: CADR to glycopeptides

Generic name	CADR
Vancomycin	LABD,[17] LABD-mimicking TEN,[18] morbilliform eruption,[19] IgE-mediated reactions, SJS/TEN, erythroderma, severe FDE, rarely vasculitis
Telavancin	Generalized redness, facial edema, hyperhidrosis, and urticaria
Dalbavancin	Urticaria
Oritavancin	Cellulitis, angioedema, EM, and leukocytoclastic vasculitis
Teicoplanin	Rarely red man syndrome

CADR - cutaneous adverse drug reaction; LABD - linear IgA bullous disease; SJS/TEN - Stevens–Johnson syndrome/toxic epidermal necrolysis; FDE - fixed drug eruptions; EM - erythema multiforme.

Macrolides

The use of macrolides for its anti-inflammatory property has increased its usage in dermatology, and it continues to be the group of choice for the treatment of gram-positive organisms in patients allergic to penicillin and few mycobacterial infections.[20]

Group-specific CADR: Acute generalized exanthematous pustulosis (AGEP).

CADR specific to macrolides have been listed in Table 33.5.

Table 33.5: CADR to macrolides

Generic name	CADR
Erythromycin	Pruritus, exanthem in <5%, occasionally SJS/TEN. Pruritus due to cholestatic hepatitis.
Azithromycin	Eosinophilic Granulomatosis with Polyangiitis (Churg–Strauss syndrome) like syndrome,[21] anaphylaxis, angioedema, DRESS, photosensitivity, LABD, toxic pustuloderma, mucositis, hypersensitivity reactions, contact dermatitis
Clarithromycin	FDE, leukocytoclastic vasculitis
Roxithromycin	Very rarely immediate hypersensitivity and TEN

CADR - cutaneous adverse drug reaction; SJS/TEN - Stevens–Johnson syndrome/toxic epidermal necrolysis; DRESS - drug reaction with eosinophilia and systemic symptoms; LABD - linear IgA bullous disease; FDE - fixed drug eruptions.

Fluoroquinolones

Fluoroquinolones (FQs) is a very essential group of drugs in the present day, especially for dermatologists, finding use in venereology, leprosy and superficial skin infections. FQs are CYP3A4 inhibitors, by virtue of which they can potentiate CADR of other drugs using the same enzyme for metabolism.

Group-specific CADR: All FQs are associated with photosensitivity (Fig. 33.6) and phototoxicity.

CADRs specific to FQ have been listed in Table 33.6.

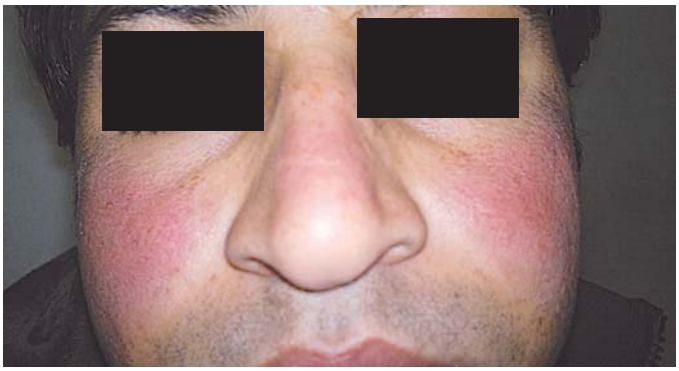

Fig. 33.6: Photosensitivity to sparfloxacin.

Table 33.6: CADR to fluoroquinolones

Generic name	CADR
Ciprofloxacin, levofloxacin, ofloxacin, norfloxacin	Urticaria (Fig. 33.7), anaphylaxis,[22] acneiform eruptions, pruritus, rarely maculopapular rash, FDE, AGEP, SJS, and TEN
Pefloxacin	Blue black pigmentation of legs[23]

CADR - cutaneous adverse drug reaction; SJS - Stevens–Johnson syndrome; TEN - toxic epidermal necrolysis; FDE - fixed drug eruptions; AGEP - acute generalized exanthematous pustulosis.

Tetracyclines

Apart from minocycline, most tetracyclines are safe with regard to CADR with few isolated case reports of other cutaneous adversities.

Group-specific CADR: The characteristic side effects are phototoxicity and photoallergic reactions. They occur usually within 5 days of drug administration although they can appear earlier. Unexposed areas may get involved as severity progresses. Among the commonly used tetracyclines, doxycycline is a more potent photosensitizer, whereas minocycline has less of a phototoxic effect. Prolonged therapy can result in vaginal candidiasis, gram-negative acne, or folliculitis due to alteration of normal bacterial flora.

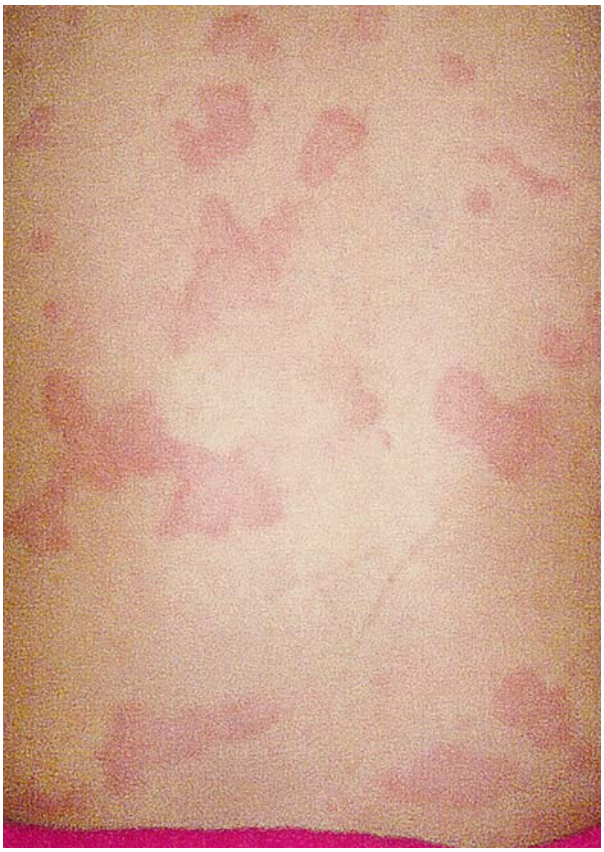

Fig. 33.7: Urticarial rash in a patient taking ciprofloxacin for sore throat.

CADR specific to tetracyclines have been listed in Table 33.7.

OTHER ANTIBACTERIALS

Aminoglycosides

Contact dermatitis from the topical aminoglycosides are the most frequent CADRs with these antibiotics.[36]

Neomycin is the most common sensitizer. Thirty percent of persons with stasis ulcers and 5% with chronic eczemas become sensitized on treatment with neomycin. Care must be taken while giving these drugs systemically as the drug can act as internal allergen and reactivate the eczema on a previously affected site. Cross-reactions among the aminoglycosides are common in patients with contact dermatitis (up to 50%) especially between drugs of deoxystreptamine group (amikacin, gentamicin, kanamycin, tobramycin, neomycin).[36]

Urticaria, maculopapular rash, fixed drug eruption (FDE), and TEN have also been reported.

Streptomycin can cause maculopapular rash, urticaria, erythema, exfoliative dermatitis, SJS, and drug hypersensitivity syndrome (DHS).

Rifamycins

- Includes rifampicin, rifabutin, and rifapentine.
- Rifampicin is a potent inducer of Cytochrome P450 enzymes with several drug interactions, requiring higher amount of dosage for the interacting drug, theoretically increasing the probability of more CADR.
- CADRs are caused by rifampicin and it is also the most common culprit among the antituberculosis drugs. Transient flushing affecting face and neck, maculopapular rash, urticaria, serum sickness-like reaction (SSLR), disseminated intravascular coagulopathy, conjunctival congestion, linear IgA bullous dermatosis SJS/TEN, pemphigus, lupus erythematous, and anaphylaxis are some of the reported reactions. These reactions are dose related.

Table 33.7: CADR to tetracyclines

Generic name	CADR	Remarks
Doxycycline	PMLE-like eruption,[25] photo-onycholysis,[26] rarely actinic granuloma, SJS, FDE	Phototoxicity presents as an exaggerated sunburn[27]
Minocycline	Hyperpigmentation of skin,[28] nails, teeth, mucosae[29]	Hyperpigmentation particularly over previous scars (Fig. 33.8. Four types of pigmentation have been described.[33] Observed in HIV positive and black ethnicity.[34]
	Serum-sickness-like reaction	
	Purpuric rash	Immune-mediated thrombocytopenia, resembling Schamberg's disease[35]
	DRESS/DHS	
	Lupus-like syndrome[30]	Associated with atypical lymphocytosis, resembling an EBV infection
	Cutaneous polyarteritis nodosa[31]	
	Drug-induced small vessel vasculitis[32]	

SJS - Stevens–Johnson syndrome; FDE - fixed drug eruptions; DRESS - drug reaction with eosinophilia and systemic symptoms; DHS - drug hypersensitivity syndrome.

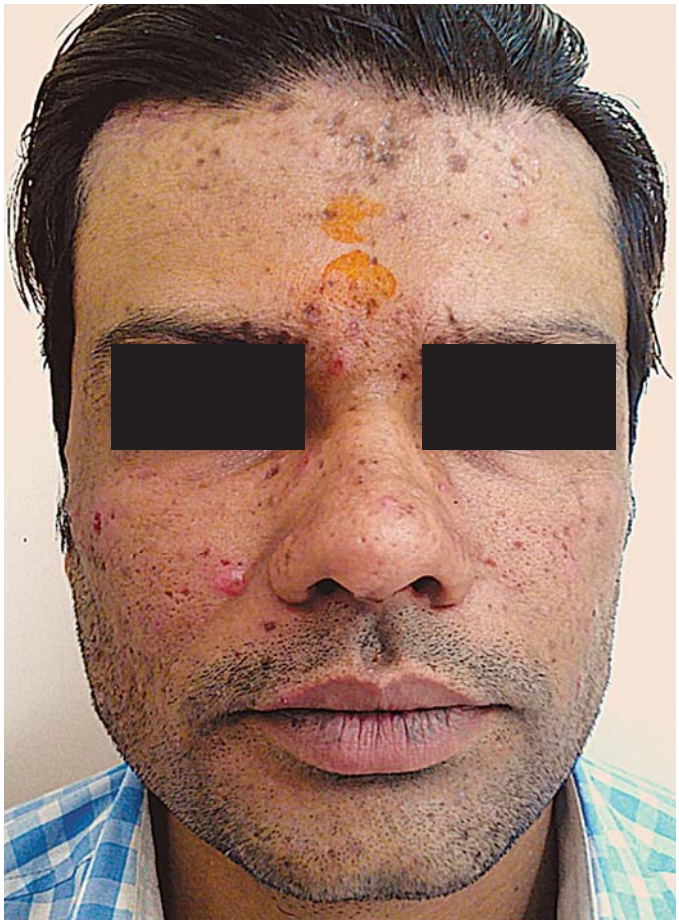

Fig. 33.8: Minocycline pigmentation. Note the pigmentation in scars. (Courtesy of Dr. Bela Shah, Ahmedabad.)

Folate Synthesis Inhibitor (Sulfonamides)

FDE, morbilliform rash, and urticaria are common group side effects. These drugs also have a higher propensity to cause SJS/TEN, EM, erythema nodosum, and photosensitivity. There can be two types of reactions:

- Immediate-type immune-mediated reactions: IgE antibodies causing urticarial rash without fever within first 3 days and re-exposure can cause life-threatening reaction. 5-methyl-3-isoxazolyl group on SMX is reportedly a key component in antibody recognition. In vitro cross-reactivity can occur with a variety of sulfonamides.
- Delayed-type reactions: Immune mediated, manifesting in 7–14 days after initiation of therapy present as fever with morbilliform, non-urticarial rash. This may progress to SJS/TEN. The incidence of SJS/TEN is between 1:1000 and 1:100,000.

  Sulfonamides can also cause drug reaction with eosinophilia and systemic symptoms (DRESS) in less than 0.1%.

Slow acetylator phenotype may be involved in pathogenesis.

Trimethoprim–sulfamethoxazole (TMP–SMX), popularly known as co-trimoxazole has a plethora of Food and Drug Administration (FDA)-approved uses in medicine. Incidence of CADR with co-trimoxazole (TMP–SMX) is the highest for any drug. Most reactions occur to the combination of TMP–SMX. SMX component is mostly responsible for the reactions. The incidence of reactions increases greatly in HIV patients.

Hypersensitivity reactions such as morbilliform rash, rash-less pruritus, DRESS (Fig. 33.9), SJS and TEN are quite common with co-trimoxazole. [37] Other rare CADRs include Sweet's syndrome, anaphylactoid reactions, erythema multiforme (Fig. 33.10), exanthems, FDE (Fig. 33.11), pustuloderma etc.

Lincosamides/Clindamycin

Topical clindamycin has produced contact dermatitis as evident in several case reports. Oral formulation has been has been associated with CADR in handful of case reports but by and large seems to be the safest option for patients with severe cutaneous adverse reactions (SCARs) needing an antibiotic cover wherein the causative drug cannot be delineated. A delayed maculopapular exanthem (7–10 days) is the most common CADR but rare cases of urticaria, angioedema, FDE, bullous lesions, AGEP, DHS, and Sweet's Syndrome have also been reported.

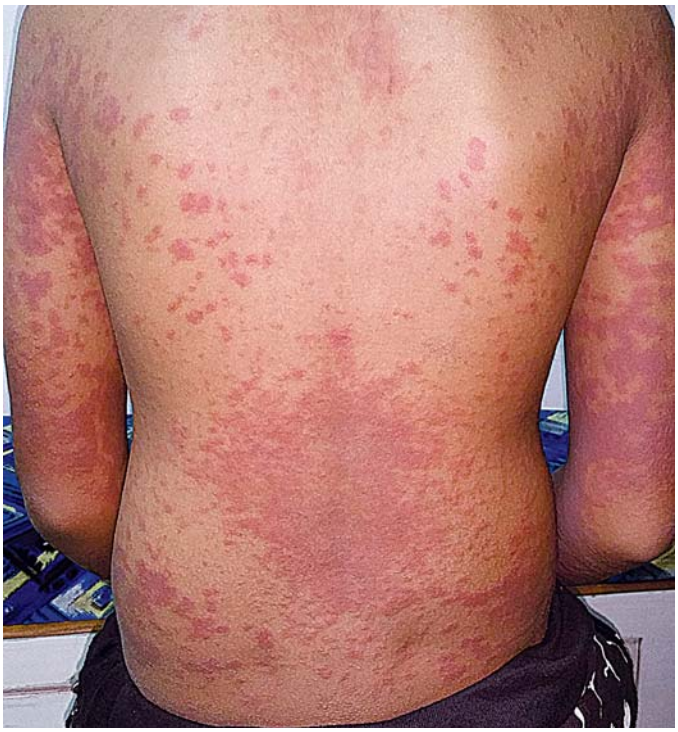

Fig. 33.9: DRESS in a child with HIV, due to co-trimoxazole.

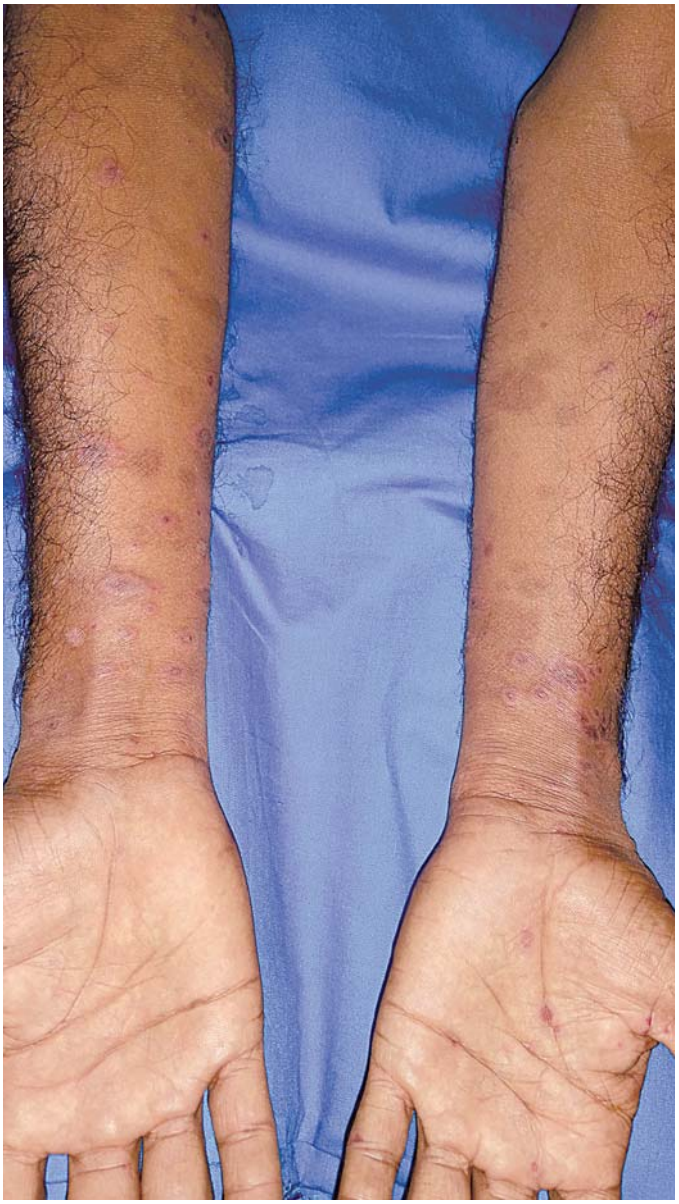

Fig. 33.10: Erythema multiforme with typical target lesions in a patient taking co-trimoxazole.

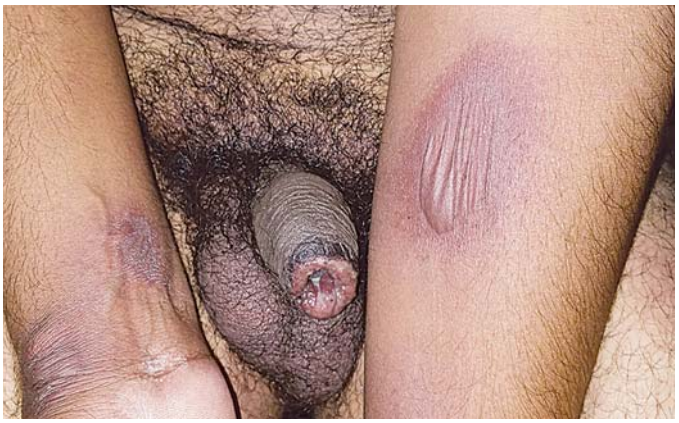

Fig. 33.11: Lesions of FDE affecting arm and genitals in a patient on co-trimoxazole.

Chloramphenicol

Anaphylaxis, urticaria, angioedema, maculopapular rash, AGEP, contact dermatitis, bullous eruption, EM, exanthemas, FDE, and SJS/TEN have all been reported due to chloramphenicol, which is now hardly used in clinical practice in most centers.

ANTIMYCOBACTERIALS

Clofazimine

It is an anti-inflammatory and anti-mycobacterial dye, well known to cause mahogany red pigmentation of skin (Fig. 33.12), occurring within 2–4 weeks of use. It is possibly due to both direct drug deposition and an induced hypermelanosis. Other important CADRs include ichthyosis, xerosis, acneiform eruptions and chromhidrosis. Nail discoloration, pedal edema and exacerbation of vitiligo have also been observed.

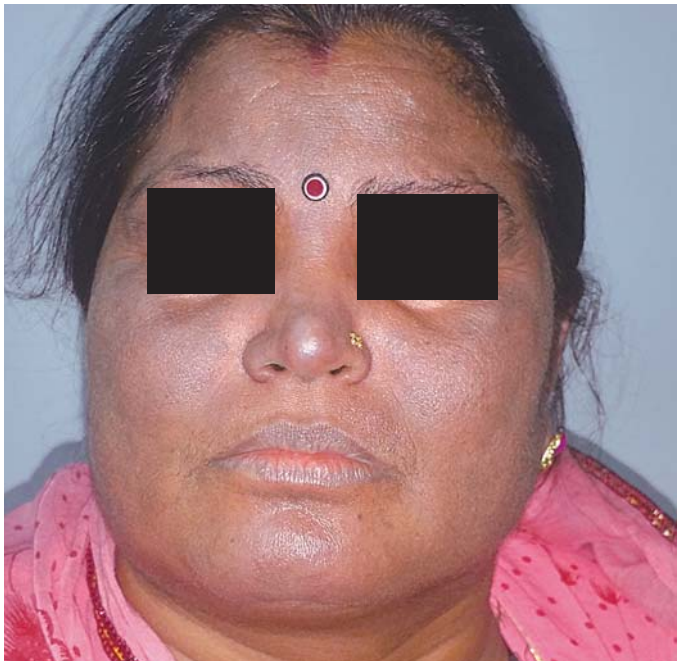

Fig. 33.12: Red-brown pigmentation to clofazimine in a patient of Hansen's disease.

Dapsone

A hypersensitivity reaction termed sulfone syndrome or dapsone syndrome develops infrequently during the first 6 weeks of treatment and is associated with high mortality, if not identified promptly. HLA-B13 screening test is now being done in some centers to identify at risk patients. This syndrome constitutes exfoliative dermatitis, fever, lymphadenopathy, malaise, and other constitutional symptoms. Other CADRs include erythema nodosum, DRESS syndrome and nail changes in the form of Beau's

lines. CADRs due to dapsone has been discussed in detail in chapter 39.

Isoniazid

Acneiform eruptions (Fig. 33.13). are seen in most patients on isoniazid (INH) and are a psychological disincentive for patients with long-term ATT. Precipitation of lupus erythematosus, pellagra, peripheral edema, and a generalized rash can be seen. Lichenoid reaction and flushing can also occur. Rarely, SJS/TEN and DRESS can occur. However, it is very difficult to pinpoint the specific incriminating drug in patients receiving medicines for TB especially in HIV/AIDS. Peripheral neuropathy of a mild nature can occur with INH and patients with preexisting peripheral neuropathy should not be prescribed this medicine.

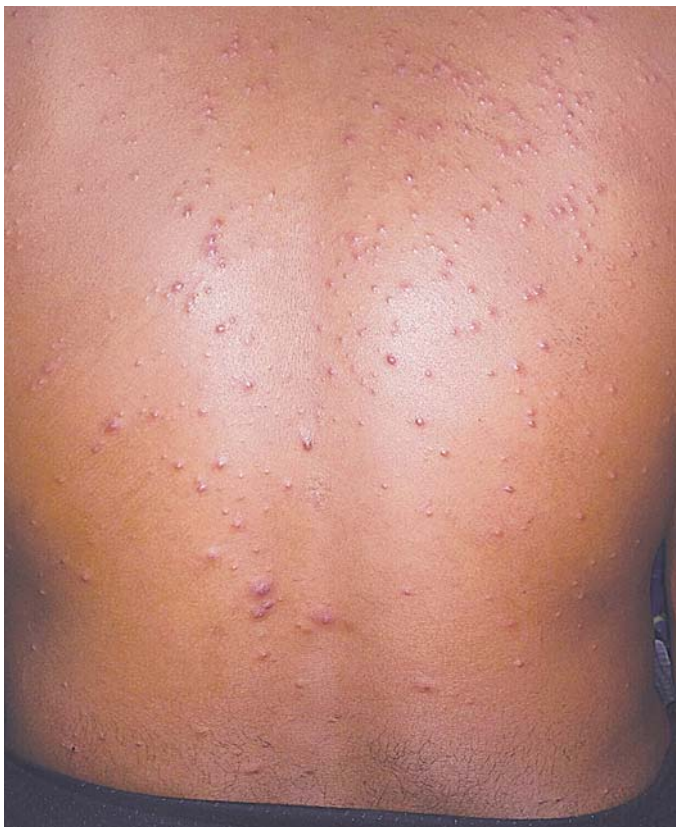

Fig. 33.13: Acneiform rash to isoniazid.

Pyrazinamide

Administration of pyrazinamide (PYZ) may cause hypersensitivity reactions such as flushing, pruritic maculopapular rash, and anaphylaxis.

Ethambutol

CADR associated with ethambutol includes hair loss, striae, urticaria, angioedema, and exfoliative dermatitis. Rarely, EM, SJS/TEN have also been reported.

ANTIFUNGALS

CADRs associated with the use of oral antifungals are of mild severity. Nevertheless, the risk associated with the use of oral antifungals is higher than the risk in non-users.[38] Paradoxical exacerbation of the dermatophytic infection has been observed in many cases with all commonly used oral antifungals.[39]

Allylamines/Terbinafine

EM and AGEP have been reported with the use of oral terbinafine. Reports of erythroderma, severe urticaria, pityriasis rosea, and worsening of preexisting psoriasis have also been described.[40] Infrequently, terbinafine have been shown to precipitate and/or exacerbate cutaneous and systemic lupus erythematosus.[41]

Azoles

Group side effect: urticaria.

Solitary case reports of TEN, SJS, AGEP, erythroderma, EM, alopecia, photosensitivity, generalized rash, pruritus, and urticaria have been seen with the use of itraconazole, ketoconazole, and fluconazole.

Cases of SJS, SJS/TEN, angioedema, and EM have been reported with the use of voriconazole. Voriconazole is also associated with photosensitivity and cases of melanoma and squamous cell carcinomas attributing to its use have been infrequently described.[42]

Griseofulvin

Urticaria is seen in more than 10% patients. However, the most disturbing CADR is photosensitivity seen in 1%–10% of patients. Precipitation of lupus erythematosus, pityriasis rosea-like rash, exanthems, and vasculitis make it a less favorable antifungal drug for present day dermatologists.

Polyenes/Amphotericin-B

No particular CADR is associated with higher incidence after the use of amphotericin-B. However, cases of exanthematous rash, anaphylactoid reactions, SJS, red man syndrome have been described.

Echinocandins/Caspofungin

Petechial rash in < 5% and facial edema in 3% may be seen in patients when administered with caspofungin. Other singular CADRs include urticaria and SJS.

ANTIVIRALS

Antivirals do not destroy their target pathogens and serve the sole purpose of inhibiting the growth and development of viruses, because of which prolonged therapies rather than short bursts are the dictum with the use of most antiviral drugs. Adverse effects seen with antivirals are thus a result of a cumulative toxicity rather than idiosyncratic as seen with antibacterials in most cases.

Antiherpetic Antivirals

Acyclovir, valacyclovir, penciclovir, and famciclovir and their congeners have been associated with scanty case reports involving cutaneous adverse effects. Acneiform eruptions due to acyclovir and its congeners have been seen in around 3% of patients. Other non-significant CADRs include urticaria, alopecia, radiation-recall dermatitis, peripheral edema, and a generalized exanthema.

Genital ulcerations, probably as a result of contact dermatitis with high urine content of drug are seen in men on induction therapy with foscarnet.[43] Diaphoresis, facial edema, ulcerative stomatitis, dyspigmentation, and a generalized rash are few other CADRs reported with the use of foscarnet.

Cidofovir, used for the treatment of *cytomegalovirus* retinitis in patients with AIDS, leads to dyspigmentation in >10%, diaphoresis in 1%–10%, and occasionally cause urticaria or a generalized exanthem.

Anti-Hepatitis Antivirals

The most common side effect of pegylated interferon (IFN)-α-2b plus ribavirin combination therapy is localized inflammatory skin lesions at the site of injection. Other CADRs include pruritic papular erythematous eruptions on the face, neck, distal limbs, dorsa of the hands, trunk, and buttocks away from the injection sites.[44]

Precipitation and/or exacerbation of psoriasis, eczema (6%), oral pemphigus, lichen planus, alopecia, sarcoidosis, lupus, FDEs, pigmentary changes, and lichenoid eruptions are some other disturbing CADRs seen with IFNs plus ribavirin therapy.[45]

Sofosbuvir, a newer antiviral, has been primarily used as a combination with other drugs such as ribavirin and IFN and hence a precise drug causality for any cutaneous eruption is not certain.

The use of adefovir has been associated with hot flushes and pruritus; however, reports exist of occasional development of SJS/TEN.

Telaprevir and boceprevir, novel protease inhibitors, recently approved for the treatment of chronic hepatitis C virus, have shown to cause DRESS.[46]

Anti-Influenza Antiviral

The use of amantadine leads to livedo reticularis in more than 50% of patients. Other rare CADRs include eczematous rash, peripheral edema, and urticaria.[47]

ANTIPROTOZOALS

Nitroimidazoles include metronidazole, tinidazole, secnidazole, ornidazole, and benznidazole.

Group side effect: FDE (Fig. 33.14).

Metronidazole: Dryness of mouth.

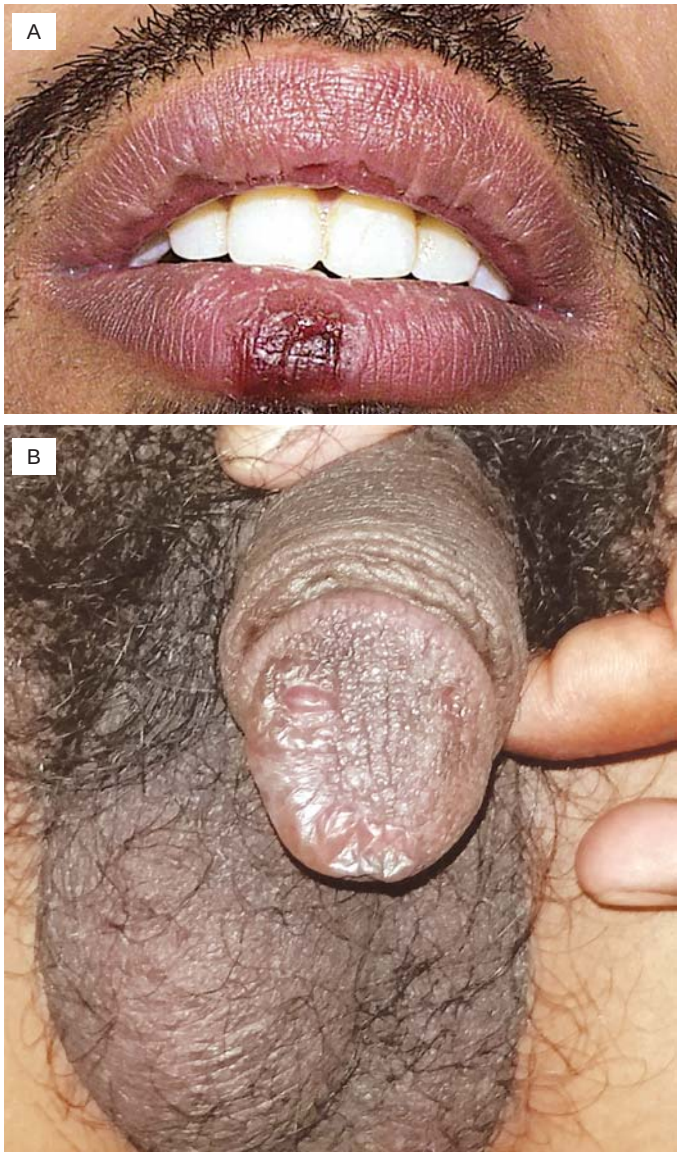

Fig. 33.14: (A) FDE lips in a patient taking metronidazole for diarrohea; (B) Bullous FDE lesions on genitals due to metronidazole.

LEARNING ESSENTIALS

- Sensitivity testing to penicillins and cephalosporins are mandatory to identify patients at risk of hypersensitivity reactions.
- Specific morphological variants of CADRs can be caused by specific group of anti-infectives and therefore a thorough knowledge may help us to pick up the offending drug in this age of polypharmacy.
- Incubation period, clinical presentation, sometimes laboratory investigations, and a thorough assessment of all drugs prescribed will help the clinician in identifying the culprit drug in most cases.

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Chapter

34

Cutaneous Adverse Drug Reactions to Retinoids and Topical Anti-Acne Agents

Niti Khunger • Abhishek Kumar

SUMMARY

- Acne is a common chronic inflammatory disease of the pilosebaceous unit, requiring long-term treatment that can lead to adverse reactions and poor treatment adherence.
- Acne is treated by a combination of topical anti-acne agents and systemic therapy, depending on the severity.
- Chief topical medications consist of topical clindamycin, tretinoin, adapalene, and benzoyl peroxide used singly or in combination.
- Irritant reactions are the most common side effects due to topical therapy.
- Systemic therapy consists of the oral retinoid-isotretinoin; systemic antibiotics, chiefly macrolides, doxycycline, and minocycline; and hormonal therapy in the form of combined oral contraceptive (COC) pills and antiandrogens, commonly spironolactone.
- Minor adverse effects with isotretinoin such as cheilitis and cutaneous xerosis are common, whereas serious adverse events such as marked hyperlipidemia, pancreatitis, and inflammatory bowel disease are rare.
- Isotretinoin is teratogenic and all precautions should be taken to avoid pregnancy 1 month before treatment, during treatment, and 1 month after stopping treatment.
- Systemic antibiotics should be used judiciously and for limited periods to prevent adverse effects and drug resistance. They should always be combined with topical treatment.
- Hormonal therapy is beneficial in patients with signs of hyperandrogenism, but should be used cautiously to avoid side effects.

INTRODUCTION

Acne is a common chronic inflammatory disease of the pilosebaceous unit, clinically characterized by a variable presence of comedones, inflammatory papules, pustules, nodules, cysts, and scars. It has high prevalence worldwide, mostly affecting adolescents, but also increasingly being seen in adults.[1] Lesions are predominantly present on the face, causing cosmetic distress, which leads to patients seeking treatment. There are broadly four categories of anti-acne medications: Topical agents, systemic antibiotics, oral retinoids, and hormonal therapy (Box 34.1). The management of acne is challenging. Being a chronic condition requiring long-term treatment, adverse reactions do occur and treatment adherence is often poor. This chapter focuses on the possible adverse effects of the topical and systemic anti-acne agents.

Box 34.1: Classification of topical anti-acne agents

Topical retinoids: Tretinoin, adapalene, tazarotene
Benzoyl peroxide
Topical antibiotics: Clindamycin, nadifloxacin, dapsone
Azelaic acid
Salicylic acid
Nicotinamide
Combinations (retinoids + antibiotics/benzoyl peroxide + antibiotics/retinoids + benzoyl peroxide)

TOPICAL AGENTS FOR ACNE

Topical Retinoids

Topical retinoids, tretinoin (0.025%, 0.05%, 0.1%) cream/gel or adapalene (0.1%, 0.3%) gel, are

considered as the mainstay of anti-acne topical therapy. They regulate gene transcription by binding to nuclear retinoid receptors. Each retinoid binds selectively to a different set of retinoic acid receptors (RARs), which confers slight differences in their efficacy and tolerability. Tretinoin binds to RAR alpha, beta, and gamma; adapalene binds to RAR gamma and tazarotene to RAR beta.[2] They normalize follicular keratinization, inhibit the development of microcomedones, help in resolution of mature comedones, and also have direct anti-inflammatory effects.[3] Application of topical retinoids also enhances the penetration of other medications, such as benzoyl peroxide and topical antibiotics, leading to a synergistic action. Thus, topical retinoids are effective in both comedonal and inflammatory acne. Yet, they should be used with utmost care as they are known for side effects. These side effects very often result in the patient discontinuing the therapy and poor compliance and adherence to treatment.

The common side effects of topical retinoids include skin irritation, burning, stinging, erythema, dryness, and peeling of skin (Fig. 34.1). Photosensitivity is a relatively uncommon complication. The irritancy potential of the retinoid depends on the rate of release on the skin. With both tretinoin and benzoyl peroxide, irritation is concentration dependent and also influenced by the delivery system, formulation, and patients' skin type.[3] In order to minimize the irritant effect, the tretinoin is microencapsulated to release the drug slowly on the skin. These newer microencapsulated tretinoin gel forms (0.04%, 0.1%) are less irritating than other formulations of tretinoin. Adapalene is reported to be better tolerated as compared to tretinoin, but this varies with the formulation of the tretinoin.[4]

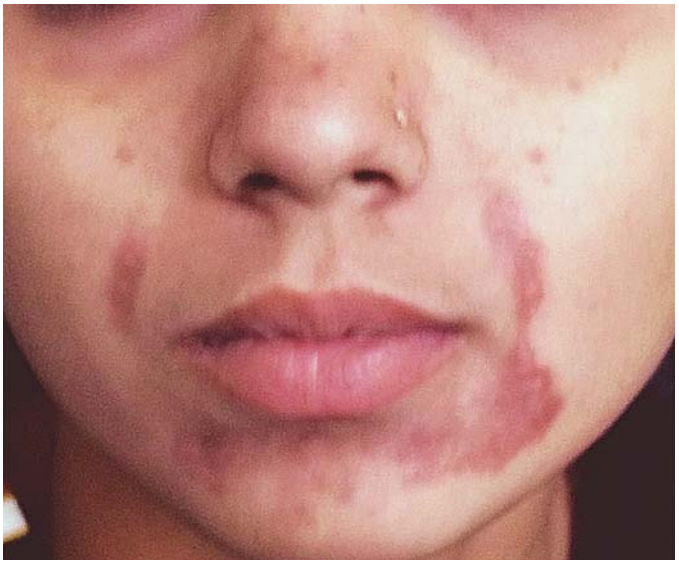

Fig. 34.1: Retinoid dermatitis following application of tretinoin 0.025% for acne.

Simultaneous use of preparations containing sulfur, salicylic acid, or resorcinol can also add up to the irritation potential of the retinoids.

Management of Side Effects

Proper selection and usage of the topical retinoids, according to the patient's skin, is the key to maximize efficacy and patient adherence.[5,6] Treatment should begin with the lowest concentration, usually in a cream-based form.[5] It should be applied at night, 20–30 minutes after the face has been washed with a mild, nonsoap cleanser. A pea-sized amount should be equally divided between two index fingers and gently applied, avoiding the periocular and perioral region. In sensitive and dry skin, the retinoid can be applied on alternate days and for short durations. Topical retinoids produce more irritation in patients with atopic eczema, rosacea and sensitive skin. Non-comedogenic moisturizers can be applied to minimize dryness and stinging. Irritation usually peaks after 2 weeks of use, and subsequently diminishes and resolves once the skin adapts, called as *retinization*. Short contact therapy is a safe and effective method for intolerant patients.[5] It involves applying the topical retinoid for a brief period of 1–3 minutes and then washing it off, increasing by 1 minute every 3 days as tolerated and without causing side effects. It was described initially for tazarotene 0.1% gel,[5] but the same technique can be used for other retinoids.

Patients should be informed that an initial flare in acne may occur in the first 2–4 weeks of use due to evolution of preexisting microcomedones. Repeated reassurance may be necessary to prevent treatment dropout. The concentration may be increased if the desired results are not obtained after 4–6 weeks. Tretinoin and adapalene are photoirritants, therefore sun exposure should be minimized through sun avoidance and the use of sunscreen or physical blockers.

Systemic Absorption and Teratogenicity

Though the teratogenic effects of oral retinoid therapy are well known, there is limited transdermal uptake of topical retinoids. Topical tretinoin penetrates the skin and accumulates in the upper dermis and has very little absorption into blood vessels or lymphatics.[7] Even prolonged application of topical tretinoin leads to minimal absorption, below the mean endogenous level of 6.6 ng/mL of all-*trans*-, 13-*cis*-retinoic acid.[8] Tretinoin and adapalene are pregnancy category C, whereas tazarotene is category X.[3] The difference in labeling stems from the fact that tazarotene is also used for psoriasis, where it can be potentially applied to a larger body surface area. Therefore, patients should be counseled on these pregnancy risks when starting a topical retinoid. In a review of pregnancy

outcomes following exposure to topical retinoids, the rate of congenital malformations following first-trimester topical retinoid exposure in 235 exposed pregnant women was compared with 444 controls[9] and no significant differences were observed between groups with regard to the rates of spontaneous abortion and minor and major birth defects. No child showed features of retinoid embryopathy.

Safety of Topical Retinoids in Children

Fixed combination of benzoyl peroxide 2.5%/adapalene 1% gel is approved for patients more than 9 years of age, and 0.05% micronized tretinoin gel for patients more than 10 years of age. All other retinoids are approved by the Food and Drug Administration (FDA) for patients more than 12 years of age.[3] It has been shown that currently retinoids in younger patients are effective and are not associated with increased irritation or risk.

Benzoyl Peroxide

Benzoyl peroxide (BP) is a topical disinfectant and acts by lowering *Propionibacterium acnes* populations by oxidative killing. It also has a mild comedolytic effect. When applied to the skin, BP breaks down into benzoic acid and hydrogen peroxide. No resistance has been reported, and the combination of BP with topical antibiotics and retinoids enhances results. BP is available as topical washes 2.5%; gels 2.5%, 5%; and creams 4%, 10%. The major side effect of BP is irritation, which can be managed with moisturizers. The other reported common side effects include erythema (Fig. 34.2) and itching. It occasionally leads to discontinuation of therapy. Irritation, staining, and bleaching of fabric are concentration dependent, higher concentrations leading to higher incidence.

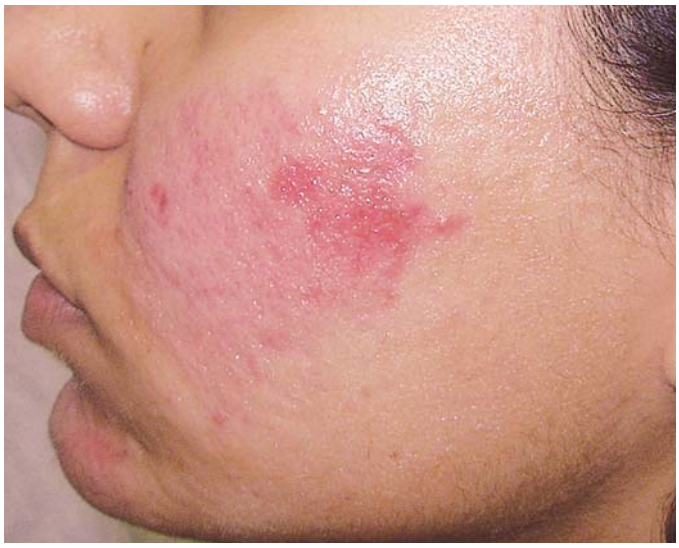

Fig. 34.2: Erythema and irritation with benzoyl peroxide 10 %.

Side effects are less frequent at a concentration of 2%–5%, rather than 10%, and with cream or lotion formulations compared with gels.[10] If irritation occurs, a lower strength or less frequent application may reduce irritation. Another possible way of reducing irritation is through usage of BP washes, where the contact time with the skin is limited. With the advent of combination therapy, the incidence of side effects related to BP has reduced significantly. Lesser side effects have been noted when BP is combined with 1% clindamycin, or adapalene. Uncommonly, contact allergy can occur. Rarely, BP has been reported to cause reticulate hyperpigmentation.[11]

BP is category C drug and is considered safe in pregnancy.

Topical Clindamycin

Topical clindamycin 1% gel has been an effective agent in acne for decades, but is no longer preferred as monotherapy due to the development of resistance. Clindamycin decreases *P. acnes* levels and also has anti-inflammatory effects. It is found to be more effective when used in combination with BP as compared to either agent alone. In addition, it reduces the potential of stinging and erythema caused by BP. Itching, burning, crusting, sense of greasiness, and contact dermatitis are some of the commonly noticed side effects with clindamycin monotherapy.[12] Though there are rare reports of diarrhea or *Clostridium difficile*–related colitis with topical clindamycin, the risk appears low.[12] Topical clindamycin alone is pregnancy category B.

Topical Dapsone

Topical dapsone 5% gel is relatively newer anti-acne agent that has been found effective in acne, possibly because of its anti-inflammatory action. Significant reduction of total lesion count is noted with use of dapsone 5% gel. Commonly noticed side effects include dryness and erythema, most of which are mild to moderate that resolve during the course of treatment and do not warrant discontinuation of treatment. In a 12 month multicenter, noncomparative, long-term study by Lucky et al., application site side effects included dryness (2.9%), rash (2.5%), and sunburn (2.3%). Burning, erythema, pruritus, aggravated acne, and peeling were also noted, which occurred in less than 2% of patients.[13] Recently, 7.5% dapsone gel as a once-daily application has also been reported to be safe and effective.[14] Co-application of BP may cause oxidation of topical dapsone causing orange-brown coloration of the skin, which can be brushed or washed off.[15] Topical dapsone 5% gel is pregnancy category C. Glucose-6-phosphate dehydrogenase testing is not required before starting topical dapsone.[3]

Nadifloxacin

Nadifloxacin is an anti-acne agent found effective against aerobic and anaerobic bacteria isolated from patients with infective skin disorders. Efficacy of nadifloxacin in inflammatory acne lesions may be attributed to its inhibitory effect on proinflammatory cytokines such as interleukin (IL)-1α, IL-6, and IL-8, which play an important role in acne pathogenesis. Although nadifloxacin has been found to be effective, combining it with other topical modalities of treatment increases its efficacy. Minor side effects such as burning and stinging can occur, but are negligible compared to other topical modalities.[16]

Azelaic Acid

Azelaic acid is a naturally occurring dicarboxylic acid analog. Azelaic acid (10% or 20%) cream or gel is an anti-acne agent, which is a mild comedolytic, antibacterial, and anti-inflammatory agent. It is useful in patients with sensitive skin or of Fitzpatrick skin types IV or more because it also has skin lightening effects. In a study by Iraji et al., approximately 3% of patients treated with 20% azelaic acid reported side effects, which mainly consisted of pruritus, burning, stinging and tingling.[17] Azelaic acid is pregnancy category B.

Salicylic Acid

Salicylic acid is a lipophilic, comedolytic agent that is available in face washes and over-the-counter creams and gels in 0.5%–2% strengths for the therapy of acne vulgaris (AV). It is likely to cause local skin peeling, burning and redness. Salicylism may occur if it is applied on large body surface areas by transdermal absorption. This potential adverse effect can occur if applied to truncal acne. Clinically, the patients have thirst, headache, lethargy, tinnitus, confusion, nausea, vomiting, diaphoresis, depression and disorientation.

Nicotinamide

Nicotinamide is used in acne due to its anti-inflammatory properties. It is used as a 4% gel–based preparation and has been found useful in mild-to-moderate acne. Use of this agent is free from the risk of resistance and has also been advised as an alternative to topical clindamycin. In a study by Khodaeiani et al., of 40 patients treated with nicotinamide 4% gel, 14 reported minor side effects with mild burning being the most common.[18]

SYSTEMIC AGENTS IN ACNE

Systemic agents used in acne include isotretinoin; antibiotics such as doxycycline and minocycline; and hormonal therapy with COC pills and anti-androgens such as spironolactone.

Isotretinoin

Isotretinoin (13-*cis*-retinoic acid) is a member of the group of drugs called retinoids that are closely related to vitamin A. It was first synthesized in 1955 and approved for the treatment of nodulocystic acne in 1982. It is one of the most effective drugs for the treatment of acne that acts on the major pathogenetic mechanisms of acne. It is sebosuppressive, inhibits sebaceous gland differentiation and proliferation, and reduces the size of sebaceous glands, thus causing suppression of sebum production. It also normalizes follicular epithelial desquamation, has an anti-inflammatory action, and inhibits growth of *P. acnes*. Further it suppresses skin dihydrotestosterone production. However, the major drawback that limits its use are the adverse effects. It has been recently postulated that the mechanism of apoptosis can explain the pharmacological action as well as the major adverse effects of isotretinoin.[19] The indications and contraindications of isotretinoin are given in Table 34.1.

Table 34.1: Indications and contraindications of isotretinoin

Indications	Contraindications
Acne (FDA Approved)	**Absolute**
Recalcitrant severe nodulocystic or inflammatory acne	Pregnancy or a women likely to become pregnant
Inadequate response (<50% improvement) after adequate course of antibiotics	Women with noncompliance with contraception
Acne that induces psychological stress, without satisfactory response to routine treatment	Nursing mothers
Marked concomitant seborrhea	
Acne variants (off-label uses)	**Relative**
Acne conglobata	Leukopenia
Acne fulminans	Moderate-to-severe elevation of cholesterol or triglycerides
Gram-negative folliculitis	Significant hepatic dysfunction
Pyoderma faciale	Significant renal dysfunction
Hidradenitis suppurativa; dissecting folliculitis of scalp	

FDA - Food and Drug Administration.

The most serious adverse effect of isotretinoin is teratogenicity and it is absolutely contraindicated in pregnancy (category X). It is important to take precautions and consent of the patient before starting therapy.

Precautions

In a woman of childbearing potential, the urine pregnancy test result should be negative and ideally should be repeated every month. A sexually active woman must practice two methods of contraception unless there is absolute abstinence or patient has undergone hysterectomy. An intrauterine device (IUD) along with an oral contraceptive or with condoms or the injection (medroxyprogesterone or Depo-Provera) may be suitable. Contraception is mandatory 1 month before therapy, during therapy, and 1 month after discontinuation of therapy.

In men, precautions to be followed are that they should not donate blood while taking isotretinoin in case the blood is given to a pregnant woman. As isotretinoin is present in semen, it may be a sensible precaution to use a condom to avoid transmission of the drug to women. However, there have been no known adverse effects on the pregnancy if a man taking isotretinoin fathers a child.

Adverse Effects and their Management[21]

The side effects of isotretinoin are dose dependent. At higher doses such as 1 mg/kg/day, nearly all patients will have some side effects, whereas at lower doses such as 0.1 mg/kg/day, most patients will not have adverse effects or they may be minimal. The adverse effects of isotretinoin are summarized in Table 34.2.

Cheilitis of the lower lip (Fig. 34.3) is very common and can be taken as a sign of drug compliance. For mild cases, an emollient with sun protection is sufficient. If the chapping persists, the lips can be moistened with a warm wet napkin before application of an emollient such as petroleum jelly. If the inflammation is severe, topical 1% hydrocortisone ointment can be prescribed for short duration of 7–10 days.

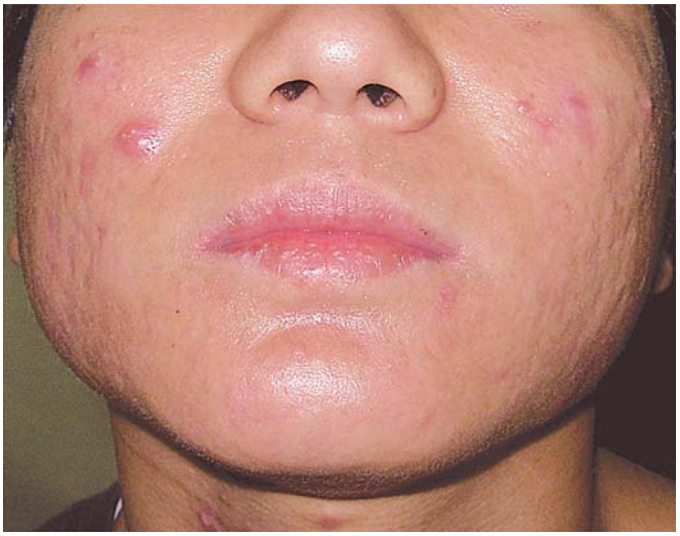

Fig. 34.3: Cheilitis following isotretinoin.

Table 34.2: Adverse effects of isotretinoin

Adverse effect	Very common (≥1/10)	Common (≥1/100, <1/10)	Rare (≥1/10,000, <1/1,000)	Very rare (≤1/10,000)
Cutaneous	• Xerosis • Localized exfoliation • Palmoplantar and digital desquamation • Pruritus • Erythematous rash • Skin fragility		• *Staphylococcus aureus* infections	• Acne fulminans • Aggravated acne (acne flare) • Facial erythema • Exanthema • Photosensitivity reaction • Pyogenic granuloma • Skin hyperpigmentation • Increased sweating
Hair		• Abnormal hair texture and dryness	• Alopecia • Telogen effluvium	• Hirsutism
Nail			• Fragility with nail softening	• Onycholysis • Nail dystrophy • Paronychia
Oral	• Cheilitis • Sore mouth and tongue • Dryness			

(Continued...)

Table 34.2: Adverse effects of isotretinoin (Continued)

Adverse effect	Very common (≥1/10)	Common (≥1/100, <1/10)	Rare (≥1/10,000, <1/1,000)	Very rare (≤1/10,000)
Nasal	• Nasal mucosa dryness • Decreased mucus secretion	• Epistaxis		
Eye	• Blepharitis • Conjunctivitis • Dry eyes • Eye irritation			• Blurred vision • Cataract • Color blindness • Contact lens intolerance • Corneal opacity • Decreased night vision • Keratitis • Papilledema • Photophobia • Visual disturbances
Ear				• Impaired hearing
Musculoskeletal	• Arthralgia • Myalgia • Back pain			• Arthritis • Calcinosis (calcification of ligaments and tendons) • Premature epiphyseal fusion • Exostosis • Hyperostosis • Osteopenia • Tendonitis
Metabolism				• Diabetes mellitus • Hyperuricemia
Blood and lymphatic system	• Anemia • Increased red blood cell sedimentation rate • Thrombocytopenia • Thrombocytosis	• Neutropenia		• Lymphadenopathy
Immune system			• Allergic skin reaction • Anaphylactic reactions • Hypersensitivity	
Psychiatric			• Depression • Aggravated depression • Aggressive tendencies • Anxiety • Mood alterations	• Abnormal behavior • Psychotic disorder • Suicidal ideation • Suicide attempt • Suicide
Nervous system		• Headache		• Benign intracranial hypertension • Pseudotumor cerebri • Convulsions • Drowsiness • Dizziness
Vascular				• Vasculitis (i.e. Wegener's granulomatosis, allergic vasculitis)

(Continued...)

Table 34.2: Adverse effects of isotretinoin (Continued)

Adverse effect	Very common (≥1/10)	Common (≥1/100, <1/10)	Rare (≥1/10,000, <1/1,000)	Very rare (≤1/10,000)
Respiratory		• Nasopharyngitis		• Bronchospasm (particularly in patients with asthma) • Hoarseness
Gastrointestinal	• Nausea • Diarrhea • Abdominal pain			• Colitis • Ileitis • Gastrointestinal hemorrhage • Hemorrhagic diarrhea • Inflammatory bowel disease • Pancreatitis
Hepatobiliary	• Increased transaminases			• Hepatitis
Renal				• Glomerulonephritis
General				• Increased formation of granulation tissue • Malaise
Investigations	• Increased triglycerides • Decreased HDL	• Increased blood cholesterol • Increased blood glucose • Hematuria • Proteinuria		• Increased creatine phosphokinase

HDL - high-density lipoprotein.

Source: Adapted from "Isotretinoin 20 mg capsules: Summary of Product Characteristics." *electronic Medicines Compendium (eMC). DataPharm Communications.*

Corneocyte dyscohesion caused by isotretinoin leads to increased water loss, dryness, and scaling, leading to xerosis and asteatotic eczematous dermatitis. It is also more common in atopics. These can be managed with noncomedogenic emollients, but the optimal approach is to use emollients prophylactically and prevent dryness from occurring. A mild soap or nonsoap cleanser or syndet bar may be prescribed. Topical mid-potent steroids such as fluticasone or mometasone ointment may be prescribed for severe cases.

Photosensitivity with isotretinoin therapy can occur and patients must be advised to avoid prolonged sun exposure during peak hours from 10 a.m. to 3 p.m. while on isotretinoin. Patients should apply a broad spectrum sunscreen with SPF 30 or higher and a lip balm that contains sunscreen, wear sun protective clothing, and use an umbrella before anticipated sun exposure. Treatment of sunburn includes use of cool tap water compresses for 10 minutes a few times a day and aspirin. If the sunburn blisters, patients should seek medical care. Nail changes in patients taking isotretinoin include nail fragility, softening, paronychia, onycholysis and granuloma pyogenic like lesions (Fig. 34.4).

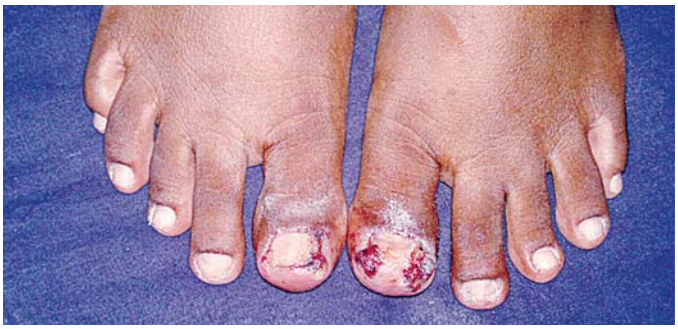

Fig. 34.4: Retinoid induced granuloma pyogenicum over toes.

Disrupted barrier function due to isotretinoin increases the chances of cutaneous infection, leading to impetigo, furunculosis, and abscesses. These should be treated with systemic antibiotics effective against *Staphylococcus aureus* and *Streptococcus*.

Flaring of acne can occur and a mild worsening may be seen before improvement starts in the first 2 weeks. Rarely, it may be severe, leading to acne fulminans. Acne fulminans is a rare side effect that presents as an abrupt onset of ulcerating acne lesions associated with fever, arthralgia, myalgia with leukocytosis, and

elevated erythrocyte sedimentation rate. It can be treated by reducing or discontinuing isotretinoin and administration of systemic corticosteroids.

Epistaxis may occur due to dryness of the nasal mucosa and blood vessel fragility. Application of Vaseline and saline nasal sprays are useful. Xerophthalmia is typically mild, but can cause irritation and blurring of vision. In these instances, contact lenses, especially hard lenses, should be avoided. Artificial tears may help. Ophthalmic consultation may be warranted if symptoms do not abate or if they are severe.

Myalgias or arthralgias occur in about 15% of isotretinoin users and is usually mild and tolerable. If it is severe, isotretinoin may need to be discontinued or the dose lowered. These side effects are usually temporary and resolve without sequelae after discontinuation of the drug.

Few early case series reported delayed wound healing or keloid formation in patients who were taking or had recently taken isotretinoin. This led to the recommendation that procedures such as dermabrasion or laser resurfacing should be delayed for 6–12 months after discontinuing isotretinoin.[22] However, recent studies did not find atypical scarring and demonstrated safety with laser hair removal, chemical peels, and other procedures.[23–25]

Raised triglyceride and cholesterol levels are common, occurring most often in patients who are obese, have diabetes or have a positive family history. Mild elevations should be monitored and usually normalize within 1–2 months after stopping treatment. Rarely, marked hypertriglyceridemia can develop and lead to acute pancreatitis. Upper abdominal pain, pain in the mid-back, nausea, vomiting, fever, jaundice and icterus are signs and symptoms of acute pancreatitis and should be diagnosed and treated promptly. A low-triglyceride diet may be helpful for patients in the high-risk groups. Pseudotumor cerebri is a rare complication that can present with headaches, nausea, vomiting and/or blurred vision that does not improve in 1–2 days. Antibiotics of the tetracycline group and supplemental vitamin A are contraindicated while the patient is on isotretinoin. Pseudotumor cerebri resolves spontaneously if it is detected early and isotretinoin is stopped. If such symptoms are ignored or not reported, the condition can slowly worsen and become potentially life-threatening. A neurologic consultation should be done in suspected cases. Fundoscopic examination for papilledema and a magnetic resonance imaging (MRI) may be necessary for further evaluation.

Fewer than 1% of patients taking isotretinoin develop inflammatory bowel disease.[7,8] Before starting therapy, ask if the patient has ever had blood in the stool, any unaccounted gastrointestinal symptoms, or a history of ulcerative colitis or Crohn's disease. If bleeding from the rectum, bloody diarrhea, or any persistent unusual gastrointestinal symptoms develop during treatment, patients must contact their physicians immediately.

Teratogenicity

Common fetal malformations include defects in the cranium and face, cleft palate, central nervous system malformations such as hydrocephalus, cerebellar malformations, microcephaly, cardiovascular defects such as tetralogy of Fallot, transposition of great vessels, and septal defects and thymic abnormalities. Abnormalities of the ear such as absence of external ear, small or absent external auditory canals, and eye abnormalities such as microphthalmia may occur. A study on pregnancy outcomes in 409 pregnancies with exposure to isotretinoin reported that 222 (54%) ended in elective abortion and 29 (7%) in spontaneous or missed abortion. Of 151 births that occurred, 72 (48%) were normal, 71 (47%) had congenital malformations, and 8 (5%) had other abnormalities.[20] This study concluded that exposure to isotretinoin during any time within the first trimester can be associated with congenital malformations.

Laboratory Monitoring

There are no guidelines for optimal cost-effective monitoring of laboratory investigations in patients on isotretinoin. A broad outline for possible investigations with their frequency that need to be carried out in patients on isotretinoin is presented in Table 34.3. A recent study on 515 patients receiving 574 courses of isotretinoin, recommended that for healthy patients on isotretinoin, a lipid panel and liver function test should be performed at baseline and after 2 months of therapy, when peak dosing is achieved.[26] Further testing should be done only if a significant abnormal value occurs. A recent review article concludes that lab values should be done baseline, then once or twice during the first 8 weeks of therapy.[27] Further testing is not required except in high-risk patients with abnormalities detected during early therapy, or patients with a history of hyperlipidemia, hypercholesterolemia, or liver disease. Closer laboratory monitoring may also be needed in patients taking other medications that can cause hepatotoxicity, bone marrow suppression, or dyslipidemia.

Systemic Antibiotics

Systemic antibiotics are recommended in the treatment of inflammatory moderate-to-severe acne.

Table 34.3: Laboratory monitoring with isotretinoin

Test	Testing frequency	Possible effect	Criteria for intervention	Action
Complete and differential blood count	Baseline and at 4 weeks	Neutropenia Lymphopenia	<1000/microL <500/microL	• Reduce dose by 50% • Repeat after 4 weeks
Fasting lipids	Baseline and at 4 weeks	Hypertriglyceridemia Pancreatitis	>8 mmol/L or increase of >5 mmol/L from baseline	• Stop drug • Repeat test in 2 weeks • Restart at 50% dose • Low-fat diet
Liver Function Test	Baseline and at 4 weeks	Deranged liver function tests (LFT)	Three times from upper limit of normal	• Repeat after 4 weeks • Review medication history
Beta hCG	Baseline and at 4 weeks	Pregnancy detection	Positive test	• Stop drug • Counsel the patient for termination
Blood sugar	Variable	Hyperglycemia	Uncontrolled hyperglycemia	• Repeat test • Closer monitoring • Diet and medication

Doxycycline and minocycline are most commonly used. Oral erythromycin and azithromycin are effective but should preferably be used when tetracyclines are contraindicated as in pregnant women and in children less than 8 years of age. Trimethoprim/sulfamethoxazole, cephalexin, and amoxicillin are second-line drugs and are used in resistant cases and patients intolerant to tetracyclines. Systemic antibiotics should not be used as monotherapy, but should be combined with topical BP or topical retinoid. They should be used for short durations, preferably not beyond 12–16 weeks. The tetracyclines and macrolide antibiotics are not only antibacterial but also have anti-inflammatory actions, by inhibiting chemotaxis and metalloproteinase activity.[28,29]

Adverse Effects

Adverse effects of systemic antibiotics in acne can occur and are usually mild and tolerable, whereas severe adverse effects are rare. Vaginal candidiasis due to prolonged use can occur with any antibiotic. Adverse events with the cyclines vary with the medication. Tetracycline and oxytetracycline are generally well tolerated. Gastrointestinal disturbances are the common side effects, particularly with doxycycline, hence they should be taken after food. Cyclines can inhibit skeletal growth in the developing fetus, hence they are contraindicated in pregnancy. They can cause discoloration of growing teeth, particularly tetracycline and therefore should be avoided in children less than 8 years of age. Photosensitivity is another complication, doxycycline being more photosensitizing (Fig. 34.5) than minocycline. This is dose dependent, being more common with higher doses, ultraviolet A (UVA) intensity, and skin type I & II according to Fitzpatrick scale.[30] Hence, sun protection is important with doxycycline. Doxycycline is primarily metabolized by the liver and can be used safely in most patients with renal impairment. Minocycline has been associated with more serious side effects, hence should be used cautiously. Pigment deposition on the skin, mucous membranes, and teeth can occur and is more common in patients taking higher doses for longer periods. Three distinct types of pigmentation occur: type I is blue-black or gray pigment on the face in areas of scarring or inflammatory lesions of acne; type II is a blue-gray pigment on normal skin on the shins and forearms; and type III is a diffuse muddy-brown discoloration in sun-exposed areas (Fig. 34.6).[31] Types I and II tend to resolve slowly over time, whereas type III can persist indefinitely. The treatment of pigmentation includes early recognition

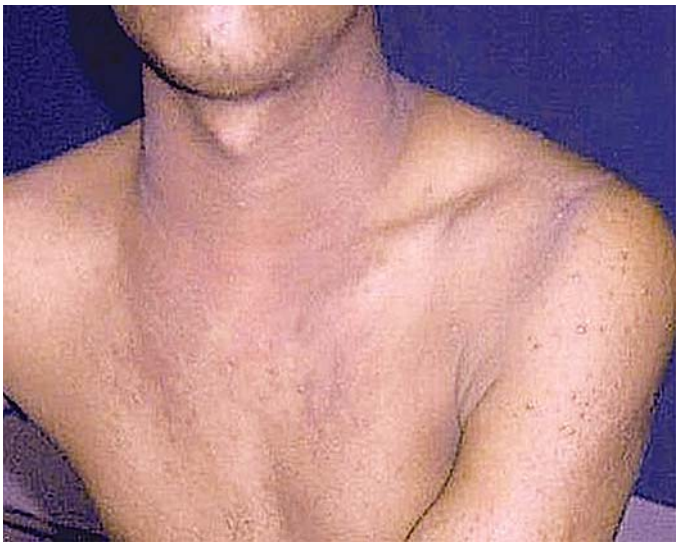

Fig. 34.5: Photodermatitis due to doxycycline in patient with acne.

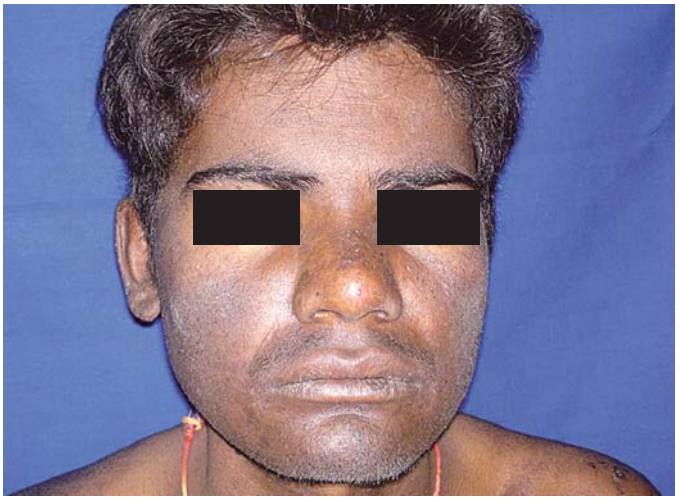

Fig. 34.6: Muddy brown pigmentation of the face in photodistribution in a patient on minocycline.

of the condition, discontinuation of the drug, sun protection, and lasers for persistent pigmentation. Tinnitus and dizziness are other side effects seen with minocycline. The rare serious adverse effects associated with minocycline include autoimmune disorders, drug-induced lupus, drug reaction with eosinophilia and systemic symptoms (DRESS), and other hypersensitivity reactions. Pseudotumor cerebri is a rare phenomenon associated with the tetracycline class of antibiotics.

The adverse events of trimethoprim/sulfamethoxazole include gastrointestinal upset, photosensitivity, and drug eruptions. Stevens–Johnson syndrome and toxic epidermal necrolysis are serious events, which are more common in patients with HIV and carry a high risk of morbidity and mortality. Hematopoietic side effects include serious blood dyscrasias, such as neutropenia, aplastic anemia, agranulocytosis, and thrombocytopenia, and hence patients on prolonged therapy should be periodically monitored with a complete blood cell count.

The macrolides are most commonly associated with gastrointestinal disturbances. Erythromycin has a higher incidence of diarrhea, nausea, and abdominal discomfort as compared to azithromycin. Macrolides have been reported to cause hepatotoxicity and cardiac conduction abnormalities. They can also decrease metabolism of cyclosporine. Penicillins and cephalosporins are associated with hypersensitivity reactions ranging from mild drug eruptions to anaphylaxis. Gastrointestinal disturbances include nausea, diarrhea and abdominal distention.

Propionibacterium Acnes Resistance

Antibiotic resistance in acne is a global phenomenon and increasing worldwide, including India.[32,33] Low concentration of the antibiotic favors emergence of antibiotic resistant *P. acnes* and may be caused by irregular treatment, prolonged antibiotic therapy, monotherapy with topical antibiotics and high sebum excretion rates. Antibiotic resistance should be suspected when there is no clinical improvement in spite of appropriate therapy and good compliance. When a relapse occurs in spite of treatment, or when the patient does not respond to multiple courses, there is a strong likelihood of antibiotic resistance. A recent study showed high resistance to erythromycin (98%), azithromycin (100%), clindamycin (90.4%), doxycycline (44.2%) and lower resistance to minocycline (1.9%) and levofloxacin (9.6%).[33]

Management of resistance includes using higher concentrations of the antibiotic or switching to another antibiotic or preferably using a nonantibiotic approach to treatment such as isotretinoin or hormonal therapy, along with topical therapy. Prevention of resistance is by using best practice guidelines such as avoiding antibiotics unless necessary, keeping treatment short and avoiding simultaneous use of dissimilar oral and topical antibiotics. BP or retinoid should be combined with a topical antibiotic and antibiotic monotherapy is not recommended to reduce incidence of drug resistance.

Hormonal Therapy

Hormonal therapy is indicated in women who show signs of hyperandrogenism, such as marked seborrhea, hirsutism, and patterned hair loss, or who have premenstrual aggravation of acne, not responding to topical therapy. COC pills containing low levels of estrogen, ethinylestradiol 35 µg with cyproterone acetate or drospirenone are the common agents used.[2,34,35] They are usually combined with antiandrogens such as spironolactone for better efficacy. All precautions should be followed before initiation of COC pills and the risk–benefit ratio should be carefully assessed.[2]

Common mild side effects of COC pills include nausea and vomiting, breast tenderness, spotting or breakthrough bleeding and weight gain. Weight gain is not seen with drospirenone. The cutaneous side effects include higher risk of developing melasma, vaginal candidiasis, photosensitivity, telangiectasia, angioma and alopecia. Erythema nodosum, purpura and the lupus erythematosus syndrome are probable adverse effects. Skin conditions such as hereditary angioedema, herpes gestationis, porphyria, hidradenitis suppurativa, seborrhea and Fox–Fordyce disease may be aggravated with COC pills.[36] The use of COC pills increases the risk of venous thromboembolism, myocardial infarction and stroke.[2,37,38] These risks are more in smokers

and in those with comorbid conditions such as obesity, diabetes and hypertension. The cardiac risk is minimal in nonsmokers, nondiabetics, and normotensives.[36] A thorough medical history and a blood pressure measurement are important before prescribing a COC pill. Increased risk of breast cancer is greatest in women less than 34 years of age, when the overall incidence of breast cancer is at its lowest. The risk of cervical cancer may also be increased in women who use COC pills.[39] In general, hormonal therapy for acne should be avoided within 2 years of menarche or in patients who are less than 14 years of age unless it is clinically warranted.[2]

PEDIATRIC ACNE[40]

Topical agents are generally considered safe in the pediatric age group. BP may be used as monotherapy and can prevent development of *P. acnes* resistance. Tretinoin gel 0.05% is approved for use in children more than 10 years of age, and combination of adapalene and BP gel 0.1%/2.5% is approved for ages 9 and above. Adapalene gel, tretinoin gel and tretinoin microsphere gel have been investigated in both open-label and blinded studies in children less than 12 years of age and are considered safe. The main adverse effects are irritant reactions. To minimize these, they may be applied for short duration and as alternate-day regimens as in adults. Transdermal absorption is minimal. In a 16-week study of 12 infants with infantile acne (mean age, 12.6 months), 0.1% adapalene improved both comedonal and inflammatory lesions in a median of 3.4 months. The side effects were mild and did not require discontinuation of treatment.[41] For moderate-to-severe inflammatory acne at any age, oral antibiotics may be used. However, tetracycline, doxycycline and minocycline should not be used in children younger than 8 years of age. For severe nodulocystic acne, scarring or refractory acne in adolescents, isotretinoin is recommended and may be used in younger patients. Counseling to avoid teen pregnancy and monitoring of potential adverse events is essential. For pubertal females with moderate-to-severe acne, hormonal therapy with COC pills may be indicated as second-line therapy. However, it is recommended that oral contraceptives for acne not associated with any endocrinologic pathology should be delayed until 1 year after menarche.

LEARNING ESSENTIALS

- Adverse reactions to topical anti-acne agents are generally mild but common, requiring a judicious approach to maximize efficacy, with minimal complications.
- Irritancy is the major drawback of these agents, particularly with topical retinoids and BP, which are the backbone for treatment of acne and for maintenance therapy.
- Isotretinoin and hormonal therapy should be used judiciously as adverse effects can rarely be serious.
- Systemic antibiotic therapy should be used only if necessary and for short duration.

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Chapter

35

Cutaneous Adverse Drug Reactions to Antihypertensives

Vishalakshi Viswanath • Vinay Gopalani

SUMMARY

Antihypertensives are one of the most commonly used drugs. A wide variety of antihypertensives are used to control hypertension of diverse etiology. Cutaneous adverse drug reactions (CADRs) to antihypertensives though not very common assumes a huge significance due to the sheer volume of prescriptions. Various cutaneous reactions have been reported with different classes of antihypertensives; however, some reaction patterns are commonly seen with specific group of drugs. It is important for the dermatologist to be aware of various drug reactions and their cross-reactivity patterns to aid in early diagnosis and provide guidance for choosing a safe alternative in a patient suffering with CADR.

INTRODUCTION

High blood pressure is prevalent in nearly 29.8% of population in India and is a leading cause of morbidity in both urban and rural settings.[1] Of all the cutaneous drug reactions, the incidence of cutaneous adverse drug reaction (CADR) due to cardiac drugs and antihypertensive drugs has been documented as 3.75% and 2.04%.[2,3] The figure assumes a huge significance when seen in context with the number of patients taking antihypertensives.

CLASSIFICATION OF ANTIHYPERTENSIVES[4,5]

A majority of hypertensive population (more than 90%) suffer with primary or essential hypertension where the cause is unknown. In contrast, secondary hypertension occurs due to various causes such as renal diseases, adrenal gland tumors, alcohol abuse, congenital blood vessel disorders, food high in sodium content, alcohol and cocaine abuse or following drug therapy [oral contraceptive pills, corticosteroids, amphetamines, decongestants, long-term nonsteroidal anti-inflammatory drug (NSAID) therapy]. Among the multitude of factors associated with primary hypertension, two factors are important: renin–angiotensin–aldosterone system (RAAS) and the disturbed electrolyte balance. Angiotensin II secreted by the RAAS causes vessel constriction and aldosterone leads to water and sodium retention. This leads to increased volume in a decreased vascular space elevating the blood pressure (Fig. 35.1). Additionally, increased sodium and decreased potassium in the body also leads to hypertension.

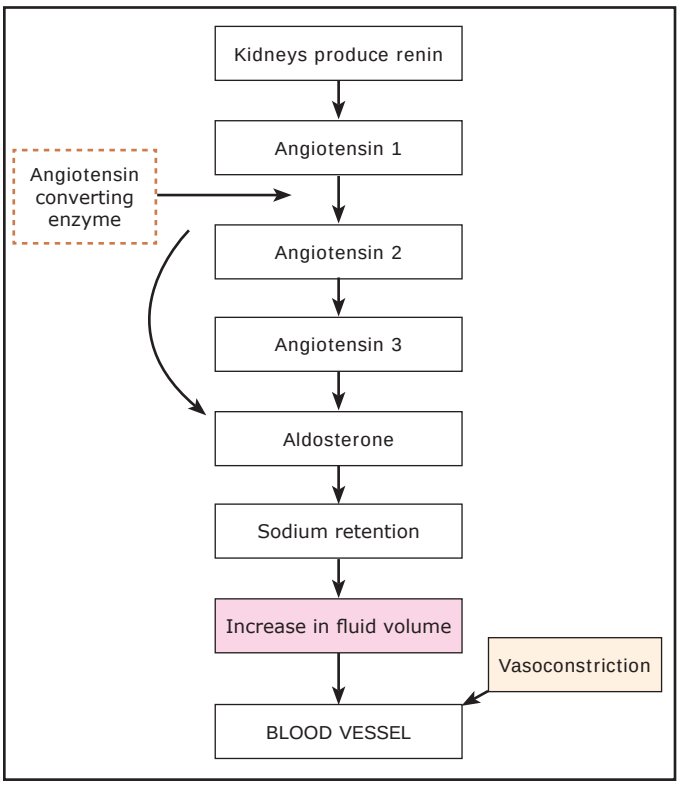

Fig. 35.1: Renin–angiotensin–aldosterone system.

Most antihypertensive drugs reduce the cardiac output and decrease the resistance in peripheral arterioles. Table 35.1 lists the common antihypertensives, classified as per their mechanism of action. It is important to realize that most drugs act by more than one mechanism of action.

Table 35.1: Classification of antihypertensives

Mechanism of action	Drugs
ACE inhibitors (drugs blocking the conversion of angiotensin 1 to angiotensin 2)	Captopril, enalapril, lisinopril, ramipril, quinapril
ARB (drugs blocking the angiotensin 2 vascular receptors)	Losartan, olmesartan, telmisartan, valsartan
Direct renin inhibitor	Aliskiren
β-adrenergic blocking agents (drugs blocking the β-adrenergic receptors)	Cardioselective β-blockers: Atenolol, metoprolol, bisoprolol Noncardioselective β-blockers: Propranolol, timolol
α-1-adrenergic blocking agents (drugs blocking the α-adrenergic receptors)	Prazosin, phentolamine
β-blockers with α-blocking activity	Carvedilol, labetalol
β-blockers with nitric oxide–mediated vasodilation	Nebivolol
Calcium channel blockers (smooth muscle dilators)	Dihydropyridines: Amlodipine, nifedipine, cilnidipine Nondihydropyridines: Verapamil, diltiazem
Diuretics	Thiazides: Hydrochlorothiazide Thiazide analog: Chlorthalidone, indapamide Loop diuretic: Furosemide Potassium sparing diuretic: Spironolactone (aldosterone antagonist), amiloride (sodium channel blocker)
Central α-adrenergic agonist (α-2 adrenergic receptor stimulants)	Clonidine, methyldopa
Direct vasodilators	Hydralazine, minoxidil
Drugs acting on postganglionic sympathetic nerve endings	Catecholamine depletors: Reserpine Adrenergic neuron blockers: Guanethidine

ACE - angiotensin-converting enzyme;
ARB - angiotensin receptor blocker.

CADRs TO ANTIHYPERTENSIVES

A wide variety of CADR have been reported with antihypertensive drugs. Urticaria, lichenoid eruption, and maculopapular exanthema were the most common adverse events in study on Indian population and were most commonly seen with atenolol and amlodipine therapy.[3] In another study on Indian population, urticaria and angioedema induced by antihypertensive drugs (enalapril, losartan, and lisinopril) were common.[6] Angiotensin-converting enzyme (ACE) inhibitors, thiazide diuretics, furosemide have been the most frequently implicated drugs in various studies.[7,8]

Table 35.2 lists the common CADR patterns seen with routinely used antihypertensives.[9,10]

COMMON ADVERSE REACTION PATTERNS SEEN WITH ANTIHYPERTENSIVES[9,10]

Various CADR patterns are common to all classes of antihypertensives as seen in Table 35.2, however, some reaction patterns are noted exclusively with a certain drug. It is important to understand the specifics of these adverse events to narrow down the culprit drug. Common CADR patterns seen in clinical practice are described in the following sections.

Maculopapular Exanthema

Maculopapular exanthema (Fig. 35.2) is a common pattern and evolves over a period of 1–3 weeks after starting the culprit drug.[3] Pruritus of variable intensity is an important differentiating feature from viral exanthema, which is usually asymptomatic or minimally pruritic.

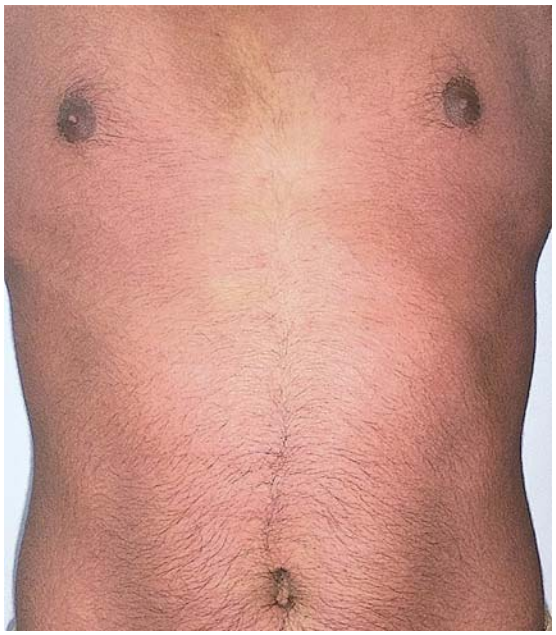

Fig. 35.2: Exanthematous rash on trunk due to telmisartan.

Table 35.2: Common reaction patterns with different classes of antihypertensives

Drug	CADR patterns	Comments
ACE inhibitors (captopril, enalapril, lisinopril, ramipril, quinapril)	Angioedema, pruritus, anaphylaxis, urticaria, vasculitis, exanthema, exfoliative dermatitis, pemphigus, lichenoid eruption, photosensitivity, SJS, TEN	Angioedema is the most common reaction seen with all drugs in this group.[11] Enalapril, lisinopril, and captopril have the maximum reported cases. Generalized pruritus is another common complaint. Captopril-induced TEN along with agranulocytosis has been reported.[12]
ARB (losartan, olmesartan, telmisartan, valsartan)	Angioedema, psoriasis/psoriasiform eruption , eczematous eruption, lymphomatoid drug eruption, vasculitis, bullous eruptions, linear IgA dermatosis, bullous pemphigoid, pemphigus foliaceus, lichenoid eruption, maculopapular eruption, EM, SJS, oral mucosal reactions, SDRIFE	Angioedema is seen with ARB, although not as commonly as with ACE inhibitors, new onset psoriasis and exacerbation of pre-existing psoriasis has been reported with losartan and valsartan. SDRIFE has been reported with telmisartan and hydrochlorothiazide.[13]
β-adrenergic blocking agents (atenolol, metoprolol, bisoprolol, propranolol, timolol, carvedilol, labetalol, nebivolol)	Psoriasis/psoriasiform, OMCS, LP/lichenoid eruption, angioedema/urticaria, drug-induced lupus erythematosus, pemphigus, vasculitis, alopecia, EM, SJS/TEN, FDE, pincer nails, xerostomia	Increase in preexisting psoriasis, therapy-resistant psoriasis, and new onset psoriasis are related to this group of drugs. Exacerbation of psoriasis was seen in 72% in a retrospective study.[14] Oral and cutaneous lichenoid eruption is noted with atenolol primarily, but also seen with other β-blockers such as propranolol, metoprolol, sotalol, and nebivolol.[15] Timolol eye drops are also associated with lichenoid reaction.[16] Alopecia is another common adverse effect.
α-1 adrenergic blocking agents (prazosin, phentolamine)	Drug-induced lupus erythematosus, LDE, pruritus, xerostomia, facial and peripheral edema	Prazosin-induced lupus erythematosus is controversial with some studies showing absence of correlation.[17]
CCBs (Dihydropyridines: Amlodipine, nifedipine, cilnidipine Nondihydropyridines: Verapamil, diltiazem)	Peripheral edema, flushing, gingival hyperplasia, gynecomastia, photosensitivity, telangiectasia hyperpigmentation, acute generalized exanthematous pustulosis, drug-induced lupus erythematosus, psoriasis/psoriasiform eruption, erythromelalgia, LP/lichenoid eruption, bullous eruption, pemphigus and bullous pemphigoid, linear IgA dermatosis, EM, SJS/TEN, erythroderma, drug hypersensitivity syndrome, purpura, eczematous eruption	Peripheral edema and flushing are most commonly reported with dihydropyridine CCB. Gingival hyperplasia is a reversible adverse effect seen most commonly in males using CCB. Nifedipine and verapamil cause maculopapular exanthema.[18] Telangiectasia on photoexposed skin are seen as early as 1 month after starting CCB and are reversible within 2 months after stopping the drug. Nifedipine, diltiazem, and verapamil can cause erythromelalgia. Amlodipine, verapamil, and nifedipine can cause lichenoid eruptions.
Diuretics Thiazides: Hydrochlorothiazide Thiazide analog: Chlorthalidone, indapamide Loop diuretic: Furosemide Potassium sparing diuretic: Spironolactone (aldosterone antagonist), amiloride (sodium channel blocker)	Photosensitivity, drug-induced lupus erythematosus, bullous eruptions, bullous pemphigoid, linear IgA dermatosis, pemphigus vulgaris, pemphigus foliaceus, pseudoporphyria, acute generalized exanthematous pustulosis, EM, SJS/TEN, vasculitis, LP/lichenoid eruptions, angioedema/urticaria, maculopapular eruption, sweet syndrome, hypertrichosis, interstitial granulomatous drug reaction	Photoallergic drug reaction and subacute cutaneous lupus erythematosus are commonly seen with hydrochlorothiazide and these patients have an increased risk of squamous cell carcinoma and malignant melanoma.[19] Furosemide and spironolactone are associated with bullous drug reactions.[20] Acetazolamide has been implicated in recurrence of pemphigus.[21] Photodistributed and nonphotodistributed lichenoid eruptions are seen with hydrochlorothiazide, spironolactone and torsemide.[22,23]

(Continued...)

Table 35.2: Common reaction patterns with different classes of antihypertensives (Continued)

Drug	CADR patterns	Comments
Central alpha adrenergic agonist (clonidine, methyldopa)	Photosensitivity, lichenoid eruption, eczematous eruption, cicatricial pemphigoid, psoriasis/psoriasiform eruption, drug-induced lupus erythematosus, xerostomia, drug rash with eosinophilia and systemic symptoms	Photosensitivity, increased risk of cutaneous cancers, oral and cutaneous lichenoid eruptions, and eczematous eruptions have been noted with methyldopa.[24,25] Psoriasiform eruptions have been documented with clonidine.[26]
Direct vasodilators (hydralazine, minoxidil)	Flushing, edema, hypertrichosis, drug-induced lupus erythematosus, vasculitis, EM, SJS/TEN, exfoliative dermatitis, generalized erythema, maculopapular eruption, drug hypersensitivity syndrome, FDE	Flushing and edema are the most common adverse events seen in this group. Hypertrichosis is commonly seen with oral and topical formulations of minoxidil.[27] Hydralazine is the most common drug implicated in drug-induced lupus erythematosus and is seen in 5%–8% patients.[28]
Drugs acting on post ganglionic sympathetic nerve endings (reserpine, guanethidine)	Flushing , peripheral edema, lupus erythematosus, pruritus , and xerostomia, alopecia, dermatitis, FDE	Cutaneous adverse events are rare with this group. Peripheral edema and drug-induced lupus are seen with reserpine.[29]

ACE - angiotensin-converting enzyme; ARB - angiotensin receptor blocker; SJS - Stevens¬Johnson syndrome; TEN - toxic epidermal necrolysis; EM - erythema multiforme; LP - lichen planus; SDRIFE - symmetrical drug-related intertriginous and flexural exanthema; OMCS - oculomucocutaneous syndrome; FDE - fixed drug eruption; LDE - lichenoid drug eruption; CCB - calcium channel blockers.

Antihypertensives causing an exanthematous drug eruption are ACE inhibitors (mainly captopril and verapamil), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), and diuretics.[18]

Withdrawal of the offending drug usually offers respite and the exanthema fades with desquamation and rarely post inflammatory hyperpigmentation over 2 weeks. Re-challenge with the offending drug invariably leads to recurrence of the exanthema.

Urticaria and Angioedema

Urticaria and angioedema can start within 3 days to 3 months after institution of the drugs.[3] The pathomechanics of drug-induced urticaria involves circulation of drug-specific IgE cross-linking with mast cells and basophils leading to release of histamine. However, angioedema due to ACE inhibitors is caused by release of bradykinin rather than histamine, and therefore, will not respond to antihistamines.[30] Potentially, life-threatening edema is seen in 0.1%–0.2% of patients on ACE inhibitors (Fig. 35.3). Other than involvement of head, face, neck and genitalia; respiratory tract involvement is seen in 20% of patients who developed angioedema while on captopril. Patients who have added comorbid factors such as C1 esterase inhibitor deficiency, asthma and old age are more prone to development of severe angioedema. Clinical improvement is seen within 24–48 hours after discontinuation of the offending drug, however, late-phase reactions are also known. Treatment of the acute phase is done by intravenous steroids and/or subcutaneous adrenaline.[31]

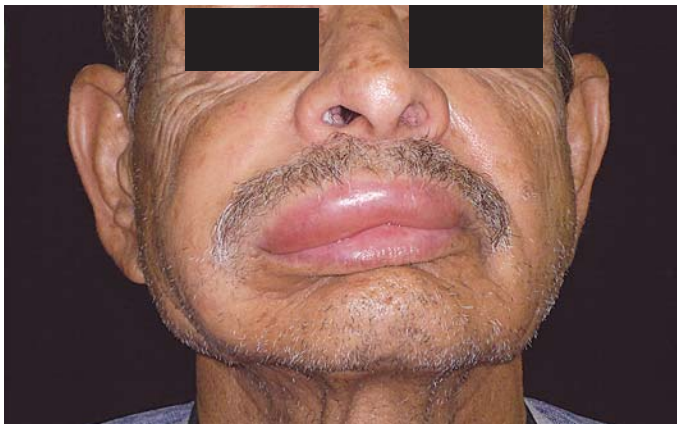

Fig. 35.3: Angioedema in a patient receiving Ramipril for last 9 months. The patient had several episodes in past. Improvement occurred after substitution with Nebivolol.

Other antihypertensives such as ARB, β-adrenergic blockers and diuretics can cause angioedema. Patients on ARB, who have previously developed angioedema with ACE inhibitors, have higher chances of developing urticaria and angioedema.[32]

Eczematous Drug Eruption

An acute or sub-acute eczematous pattern (Fig. 35.4) of drug allergy is usually seen in patients after oral administration of drug to which the patient had been previously sensitized topically. A new concept theorizes direct recognition of small chemically inert drug molecules by T cells leading to direct systemic sensitization without prior history of topical use.[33]

Eczematization is seen after 7–14 days of drug initiation. It manifests as acute eczema in the flexural areas and gradually generalizes. Rarely, it may evolve into an exfoliative dermatitis. Drug-induced baboon syndrome, also known as symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) shows a characteristic involvement of the gluteal and anogenital area and sometimes other areas such as axillae, knees, elbows and neck.[34] Eczematous eruptions are seen with CCBs and thiazides. SDRIFE has been reported with telmisartan-hydrochlorothiazide combination.[13] Photoallergic reaction manifesting as eczematous drug eruptions are commonly seen with thiazide diuretics.

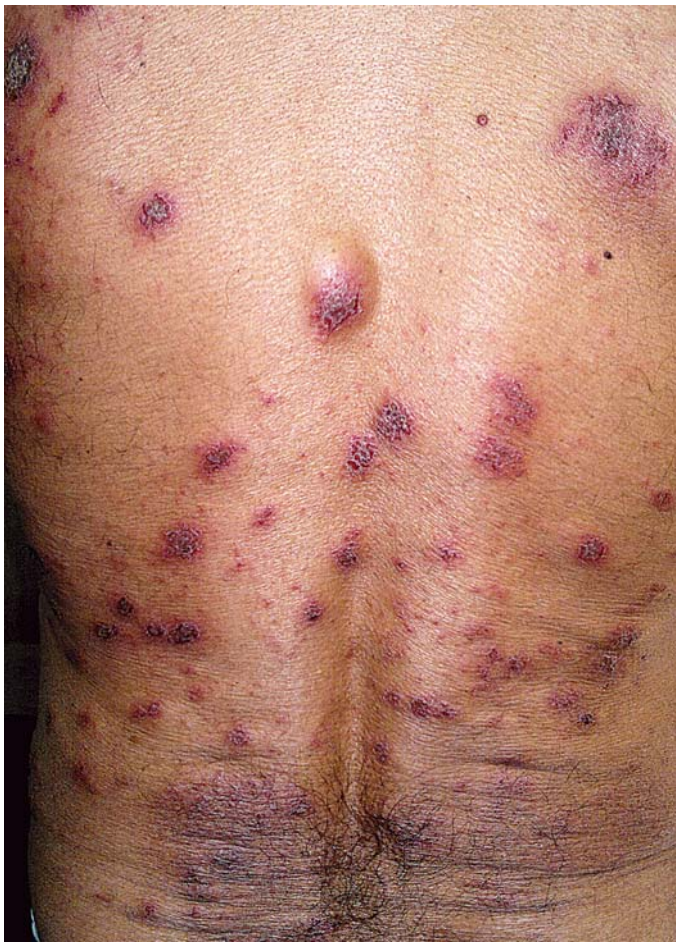

Fig. 35.4: Eczematous rash on trunk in an elderly patient on amlodipine.

Lichenoid Drug Eruption

Lichenoid drug eruption (LDE) is the second most common adverse event seen with antihypertensives. The latency period varies from months to years and the average latency period was noted to be 19.6 months in a study on Indian population.[3] Clinically, LDE may be indistinguishable from idiopathic lichen planus (LP). Distribution of lesions in photo-exposed areas (Fig. 35.5) along with histologically, higher number of clustered necrotic keratinocytes, eosinophilic and plasma cell infiltrate may point to LDE.[30]

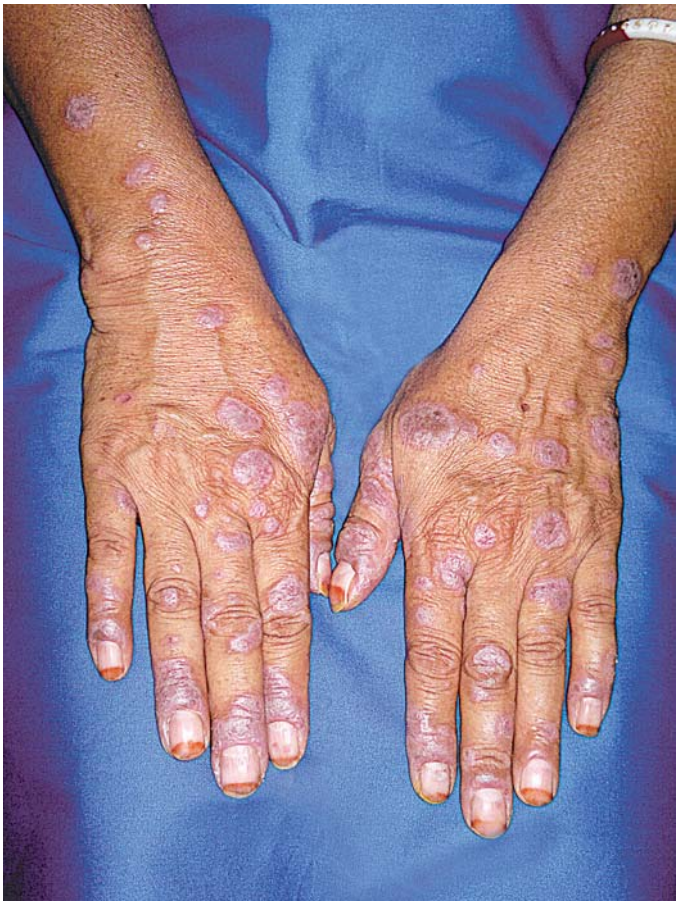

Fig. 35.5: Lichenoid reaction in a patient taking amlodipine.

Thiazide diuretics, β-blockers, ACE inhibitors, and methyldopa are known to cause LDE. LDE in a photosensitive distribution has been reported with thiazide diuretics.[22]

Drug-Induced Psoriasis[10,35]

Drugs can affect psoriasis by multiple pathways. It can initiate psoriasis, induce new lesions in pre-existing case of psoriasis, exacerbate existing lesions, and induce resistance to therapy. In cases of drug-induced psoriasis, discontinuation of drug stops the progress

of the disease whereas in cases of exacerbation, the disease process continues beyond the stoppage of drugs. Drug-induced psoriasis (Fig. 35.6) clinically manifests as pustular variant of psoriasis without nail and joint involvement and there is an absence of Munro's microabscesses with few macrophages and mild vascular changes.[36] The average latency period from antihypertensive initiation can range from few weeks as in case of ACE inhibitors to up to 2 years as seen with β-blockers.[3] Theoretically, β-blockers induce psoriasis by alteration in the cyclic adenosine monophosphate (cAMP) pathway which in turns leads to altered cell differentiation and increased cell proliferation.[36] The risk of psoriasis increases with the duration of β-blocker use.[37] Other antihypertensives that can exacerbate psoriasis include CCB and ARB. Remission is usually seen within few weeks to months after stopping the drug.

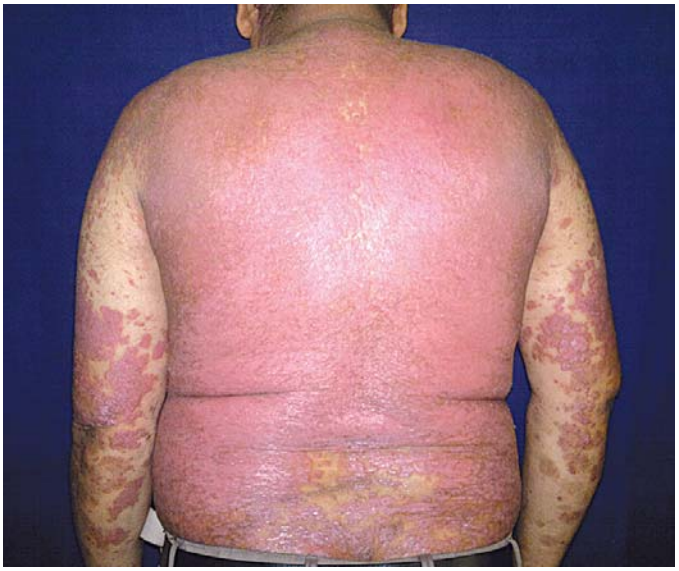

Fig. 35.6: Psoriasiform rash in a patient on captopril.

Bullous Drug Eruption[35]

Drug- induced bullous reactions (Fig. 35.7) include a variety of vesiculobullous conditions such as drug-induced bullous pemphigoid (DIBP), drug-induced pemphigus vulgaris (DIPV), and linear IgA bullous dermatosis (LABD). DIBP can be indistinguishable from classical bullous pemphigoid and therefore, in all cases of bullous pemphigoid, the possibility of drug as an etiological factor should be considered. Furosemide and spironolactone are classical inciters of DIBP and the eruption can be seen up to 3 months after ingestion of the inciting drug.

DIP can be caused due to thiol drugs, phenol drugs, or nonthiol nonylphenol drugs. ACE inhibitors belong to the thiol group whereas CCB and propranolol belong to the nonthiol group. Thiol drugs cause acantholysis by various mechanisms such as inhibition of enzymes that aggregate keratinocytes; activation of enzymes, such as plasminogen activator, which disaggregate keratinocytes; disruption of cell adhesion by formation of thiol-cysteine bonds instead of cysteine-cysteine bonds; and formation of a neoantigen by an immunological reaction. CCBs cause pemphigus because calcium is needed for the activity of enzymes that play a role in keratogenesis, and desmogleins are calcium dependent. The lesions in DIP can begin from several weeks to months after initiation of the drug. Pemphigus foliaceus-like pattern is more common and seen with DIP due to thiol group; whereas pemphigus vulgaris pattern is seen with nonthiol group. Remission occurs spontaneously in more than 50% of patients where the inciting agent has a thiol moiety and in only 15% of cases with the other drugs. Interferon (IFN)-γ release assay may be useful in identifying the drug.[38,39]

LABD can be associated with drugs such as captopril and furosemide and appear within 1–15 days after starting the drugs. The condition can be indistinguishable from the idiopathic version of the disease.

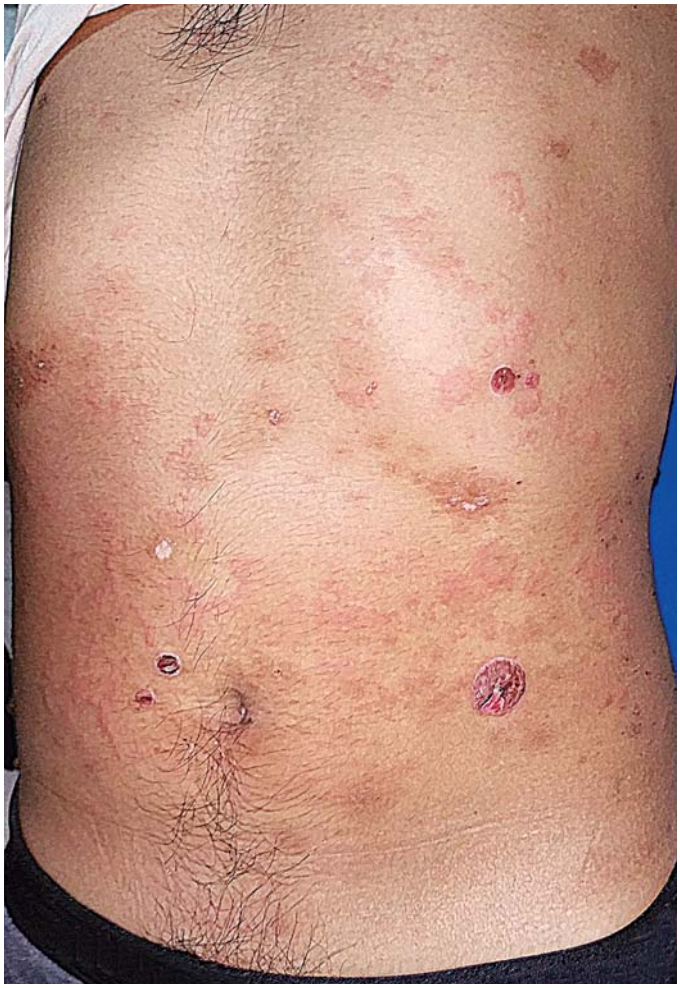

Fig. 35.7: Bullous pemphigoid like drug rash in a patient on furosemide.

Vasculitis[10,35]

Drugs are the causative factors in 10% of cases of vasculitis. Usually the smaller vessels are involved, however, medium vessel involvement is also known. The lesions begin 1–3 weeks after starting the drug and can present as purpuric papules, urticarial wheals, hemorrhagic blisters, and ulcers. Systemic features such as fever and arthralgia may also be associated.

ACE Inhibitors, β-blockers, hydralazine, furosemide, and thiazide diuretics can cause vasculitis. Nonvasculitic telangiectasia is seen with CCB. Hydralazine is associated with antimyeloperoxidase antibody formation and antineutrophil cytoplasmic autoantibody (ANCA) vasculitis.

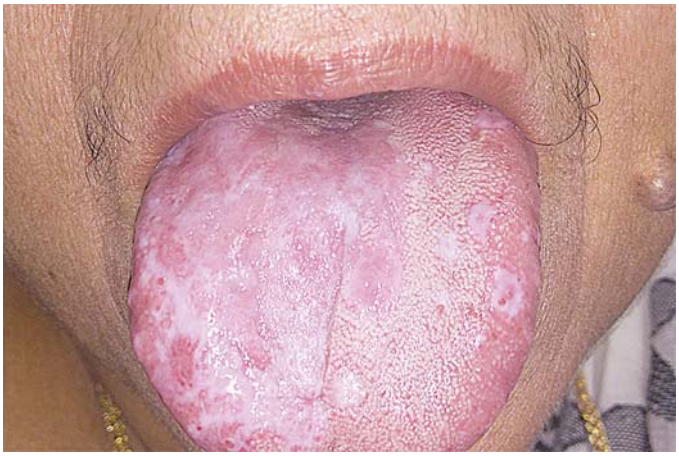

Fig. 35.8: Oral lichenoid lesions in a hypertensive patient on amlodipine and telmisartan.

Oral Reaction Patterns[40]

A wide variety of oral adverse reactions may be seen with antihypertensives (Table 35.3). The common oral mucosal adverse effects include dry mouth, taste disturbance, burning mouth syndrome, LP (Fig. 35.8), and gingival hyperplasia. Dry mouth is the most common CADR and in turn can lead to an increased incidence of dental caries and oral candidiasis. Burning mouth syndrome (also known as scalded mouth syndrome) is a chronic burning sensation in some area of the mouth lasting for more than 4–6 months in the absence of a specific oral lesion. It is a class effect of antihypertensives that act on the renin–angiotensin system (ACE inhibitors and ARBs). Gingival hyperplasia is another class adverse effect seen primarily with CCBs. It may be localized or generalized and maintaining optimal oral hygiene may be helpful.

Table 35.3: Oral reaction patterns seen with antihypertensives

Antihypertensive group	Adverse effect and implicated drugs and classes
α-adrenergic blocking agents	• Class adverse effect: Dry mouth
β-adrenergic blocking agents	• Class adverse effect: Dry mouth, angioedema • LP seen with atenolol, oxprenolol, propranolol • Aphthae and ulcerations seen with labetalol • Oculomucocutaneous syndrome seen with practolol • Mouth paresthesia seen with sublingual propranolol[41]
ACE inhibitors	• Class adverse effect: Angioedema • Aphthae/ulceration: Captopril • Dry mouth: Lisinopril • LP: Captopril • Pemphigus: Captopril • Burning mouth syndrome: Captopril, enalapril, and lisinopril[42] • Taste disturbance: Captopril, enalapril
ARB	• Angioedema: Losartan • Burning mouth syndrome: Candesartan, eprosartan[42]
CCBs	• Class adverse effect: Dry mouth, taste disturbance, and gingival hyperplasia[43] • Angioedema: Nifedipine, diltiazem • Aphthae/ulceration: Diltiazem/verapamil
Diuretics	• Class adverse effect: Dry mouth[44] • LP: Spironolactone, furosemide • Taste disturbances: Amiloride, spironolactone

ACE - angiotensin-converting enzyme; ARB - angiotensin receptor blocker; LP - lichen planus; CCB - calcium channel blocker.

Drug-Induced Hair and Nail Changes

Drug-induced chronic diffuse telogen hair loss (CDTHL) is seen with *β*-blockers and ACE inhibitors; it evolves over a period of 6–12 weeks after the drug has been administered and continues till the drug is administered. The possible pathomechanism is an early anagen release by the culprit drug.[45] Oral minoxidil causes stimulation of hair growth by shortening telogen and causing premature entry of resting hair follicles into anagen.[46]

Use of *β*-blockers is associated with nail damage secondary to digital ischemia. This occurs due to lack of peripheral vasodilatation in response to reduced cardiac output in cases of noncardioselective *β*-blockers such as propranolol.[47] Finger nail clubbing and discoloration has been reported with use of losartan for a month. The symptoms persisted despite change of drug to valsartan and subsided only after changing the drug to captopril.[48] Use of topical timolol eye drops was associated with nail psoriasis due to holding the lower eyelid while administering the eye drops. The lesions resolved after discontinuation of use of eye drops.[49]

Drug-Induced Sexual Dysfunction

β-blockers, diuretics, and central *a*-adrenergic agonist are associated with erectile dysfunction.[50] However, losartan has a positive effect on erectile dysfunction.[51] Sexual dysfunction in females is associated with the use of *β*-blockers but diuretics, CCBs, ACE inhibitors or ARBs are not associated with sexual dysfunction.[52]

Drug-Induced Malignancies

Many antihypertensives are photosensitizing and may also have the potential to cause skin cancers. In a population based database study, it was found that chronic users of antihypertensives belonging to the ARB group had a higher risk of malignant melanoma and patients on long-term diuretics had a higher risk of developing squamous cell carcinoma.[53] These findings were corroborated in another database study and an increased risk of squamous cell and basal cell carcinomas was noted with ARB and ACE inhibitors.[54]

INVESTIGATIONS[10]

A detailed clinical history documenting the case chronologically to determine the temporal relationship between the onset of eruption and drug intake (in the last few weeks or months) is the ideal method of diagnosing a CADR. Common CADR to antihypertensives based on the onset of drug eruption and likely culprit drug is outlined in Fig. 35.9. Using

Morphological pattern of CADR	Time between drug institution and development of CADR	Culprit drug
Urticaria and angioedema	3 days to 3 months	ACE inhibitors, ARB, β-blockers, Diuretics
Maculopapular exanthema	1 week to 3 weeks	ACE, ARB, CCB, Diuretics
Lichenoid Drug eruption	Months to years	Thiazide, β-blockers, ACE, Methyl dopa
Drug induced psoriasis	Few weeks (ACE inhibitors) to years (β-blockers)	β-blockers, ACE, CCB, ARB
Drug induced eczema	1 week to 2 weeks	CCB, Thiazide
Bullous drug eruptions	DIBP: 3 months DIP: several weeks to months LABD: 1-15 days	DIBP: Furosemide, Spironolactone DIP: Nifedipine, Propranolol LABD: Captopril, Furosemide
Vasculitis	1 week to 3 weeks	ACE inhibitors, β-blockers, Hydralazine, Furosemide, Thiazide

Fig. 35.9: Algorithm for locating the culprit drug based on morphology of lesions and the latency period.

the Naranjo adverse drug reaction probability scale is helpful in reaching to a conclusion.[55] Asking leading questions about a history of similar reaction may be helpful. History of fever and lymphadenopathy may indicate a more serious drug reaction. Improvement of symptoms after drug withdrawal is a definitive sign of CADR.

The diagnosis of CADR is chiefly clinical, but can be aided by investigations. Based on the clinical pattern, a skin biopsy may be helpful, especially in cases of drug-induced vasculitis, eczematous eruptions, and LDE. Skin tests may not be conclusive, however, may be helpful. Prick or scratch tests and intradermal tests can be done for type I immunologic reactions, and intradermal tests or patch tests for type IV immunologic reactions. Photopatch testing may be helpful in diagnosing photoallergic drug reaction.

Serum allergy tests are generally not helpful and can be used for type 1 immunological reactions. IFN-γ release assay may be a useful adjunct for diagnosis. Oral rechallenge may be the gold standard to prove an allergic reaction; however, it can be done only in selected local cutaneous reactions and is contraindicated in severe cutaneous drug reactions, anaphylactic reactions, and drugs with potential to cause anaphylactic or anaphylactoid reactions.

MANAGEMENT[10]

The management of adverse reactions to antihypertensives remains the same as with other CADRs. The primary step is to stop the suspected drug. It is important to remember that the new drug introduced should not cross-react with the culprit drug. The cross-reactivity pattern of common antihypertensives has been outlined in Table 35.4.[56,57]

For mild exanthema, symptomatic treatment with antihistamines and topical soothing agents such as calamine may suffice. Severe cases warrant the use of systemic corticosteroids, especially in reaction patterns such as drug hypersensitivity syndrome (DHS). In toxic epidermal necrolysis (TEN) (uncommonly seen with antihypertensives), the use of steroids and immunosuppressants such as cyclosporine is still controversial.

Table 35.4: Cross-reactivity of commonly used antihypertensives

Drug	Cross-reactive drug/groups
ARBs	ACE inhibitors
β-blockers	Between cardioselective and noncardioselective β-blockers
CCBs	Possibly between different subgroups: seen with diltiazem and nifedipine; diltiazem and verapamil; diltiazem and amlodipine
Diuretics	Possibly between sulfonamide antibiotics, loop or thiazide diuretics, and oral hypoglycemics

ACE - angiotensin-converting enzyme; ARB - angiotensin receptor blocker; CCB - calcium channel blocker.

LEARNING ESSENTIALS

- Various CADR patterns are common to all classes of antihypertensives, however, some reaction patterns are noted exclusively with certain drugs/classes.
- Urticaria, lichenoid eruption, maculopapular exanthema and a wide variety of oral adverse reactions are common CADR patterns seen with antihypertensives. These drugs can initiate psoriasis, induce new lesions in preexisting cases, exacerbate existing lesions, and also induce resistance to therapy. Drug-induced bullous eruptions (DIBP, DIP, and DILABD), DHS, Stevens–Johnson syndrome (SJS)/TEN can occur with antihypertensives, but is uncommon.
- ACE inhibitors, thiazide diuretics, and furosemide are frequently implicated antihypertensive drugs causing CADR.
- The temporal relationship between institution of drug and onset of reaction helps in diagnosis.
- Besides withdrawal of the offending drug, the cross-reactivity patterns amongst various classes of antihypertensives should be considered before introducing a new drug in a suspected case of CADR.

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Chapter

36

Cutaneous Adverse Drug Reactions to Antiepileptic Drugs

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SUMMARY

Antiepileptic drugs (AEDs) are one of the most commonly prescribed drugs and a common cause of cutaneous adverse drug reactions (CADRs), particularly serious ones, in India. While aromatic anticonvulsants such as phenytoin, phenobarbitone, carbamazepine, and lamotrigine are the most frequently implicated drugs, newer AEDs such as oxcarbazepine, felbamate, primidone and zonisamide have also been implicated in severe CADRs. Common drug reaction pattern by AEDs include maculopapular rash, Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), serum sickness–like reactions (SSLRs) and acute generalized exanthematous pustulosis (AGEP). The reaction pattern by AEDs may be due to excessive drug–induced toxicity, metabolic idiosyncrasy due to locally formed reactive metabolites and immunological idiosyncrasy due to neoantigen formation to intermediate metabolites. Cross-reactivity with carbamazepine is observed with phenytoin, phenobarbital, lamotrigine and oxcarbazepine.

INTRODUCTION

In India, cutaneous adverse drug reactions (CADRs) account for 2%–5% of all inpatients, whereas they affect 2.6% of outpatients.[1] Epilepsy is one of the most common diseases prevalent in India. Of the 50 million people living with epilepsy worldwide, 10 million reside in India. Antiepileptic drugs are among the most common group of drugs implicated in CADRs. A classification of AEDs is given in Table 36.1.

The spectrum of CADRs ranges from a transient maculopapular rash to life-threatening conditions such as drug reaction with eosinophilia and systemic symptoms (DRESS) and toxic epidermal necrolysis (TEN). In a study on CADRs, the most common types of CADR patterns were maculopapular rash (34.6%), fixed drug eruption (FDE) (30%), and urticaria (14%).[2] The drugs most often incriminated were, antimicrobials (42.6%), anticonvulsants (22.2%), and nonsteroidal anti-inflammatory drugs (NSAIDs: 18%). Anticonvulsants were implicated in 41.6% of maculopapular rashes.[2.] Among AEDs, carbamazepine and phenytoin were the most common offending agents.[2] In another study, antimicrobials (34.10%), anticonvulsants (32.88%), and anti-inflammatory drugs (21.51%) were the most common drug groups reported to cause CADRs.[3]

The risk of severe or life-threatening CADRs is estimated to be 20 cases in 100,000 for phenobarbitone, 90 in 100,000 for phenytoin and 60 in 100,000 for carbamazepine.[4] The estimated incidence of Stevens–Johnson syndrome (SJS)/TEN is 1–6 cases in 10,000 among European ancestry who are exposed to the drug. Aromatic anticonvulsants (e.g. phenytoin, phenobarbitone, carbamazepine, and lamotrigine) are the most commonly implicated drugs.[4] The rate of an AED rash is approximately five times greater in patients with another AED rash (8.8%) vs those without (1.7%). Potentially severe and life-threatening CADRs (including SJS and TEN) are estimated to occur in 1 in 1000 adults and 1 in 50–100 children.[5]

Among newer anticonvulsants, only felbamate, lamotrigine and clobazam have been implicated in severe CADRs. Felbamate is reported to induce CADRs in approximately 5%–9% of patients. Mild CADRs have occurred with zonisamide and vigabatrin. CADRs to gabapentin, topiramate, and tiagabine used as single AEDs have not been reported in the literature. Zonisamide causes SJS/TEN at the rate of 46 cases per million. Incidence of

Table 36.1: Classification of antiepileptic drugs

Sodium channel blockers	GABAergic	Glutamate blockers	Others
Phenytoin, fosphenytoin, carbamazepine, oxcarbazepine, eslicarbazepine, lamotrigine, zonisamide, lacosamide	**GABA agonist**	Felbamate, topiramate	Levetiracetam, gabapentin
	Barbiturate, benzodiazepines		
	Uptake inhibitor		
	Tiagabine, vigabatrin		
	Increases GABA		
	Valproate		

GABA - γ-aminobutyric acid.

rash by gabapentin is 0.5%. Oxcarbazepine, which does not form the 10,11-epoxide metabolite, has been reported to cause exanthematous reactions.[1]

Common drug reaction patterns to AEDs include maculopapular rash, SJS/TEN, DRESS, serum sickness–like reactions (SSLRs), and acute generalized exanthematous pustulosis (AGEP) (Table 36.2).[6] Some of the uncommon cutaneous drug reaction patterns are given in Table 36.3.[6] AEDs are among the most common culprits in causing CADRs with systemic involvement[7] (Box 36.1).

Box 36.1: Cutaneous adverse drug reactions with cutaneous and systemic involvement

- Toxic epidermal necrolysis (TEN)
- Drug hypersensitivity syndrome (DHS)
- Stevens–Johnson syndrome (SJS)
- Serum sickness–like reactions (SSLRs)
- Acute generalized exanthematous pustulosis (AGEP)

Table 36.2: Common drug reaction patterns to antiepileptic drugs

SJS/TEN	Phenytoin, carbamazepine, lamotrigine, trimethadione
Hypersensitivity syndromes	Phenytoin, carbamazepine, lamotrigine
Morbilliform eruptions	Phenytoin, carbamazepine, barbiturates, lamotrigine
FDE	Phenytoin, carbamazepine, barbiturates, lamotrigine
Urticarial	Phenytoin, carbamazepine, barbiturates, lamotrigine
AGEP	Phenytoin
LE-like syndrome	Carbamazepine, phenytoin, trimethadione, barbiturates, fosphenytoin

SJS - Stevens–Johnson syndrome; TEN - toxic epidermal necrolysis; FDE - fixed drug eruption; AGEP - acute generalized exanthematous pustulosis; LE-like syndrome, lupus erythematosus–like syndrome.

Table 36.3: Uncommon drug reaction patterns to antiepileptic drugs

Peripheral neuropathy, heel pad thickening, pellagra, hirsutism	Phenytoin
Gingival hyperplasia, fetal hydantoin syndrome	Phenytoin, fosphenytoin
IgA bullous dermatoses	Phenytoin, fosphenytoin
Eosinophilic fasciitis, Peyronie's fibromatosis, porphyria cutanea tarda, polymyositis	Phenytoin
Acne keloidalis–like lesions, dyssebacia, facial pustules	Phenytoin
Vasculitis	Phenytoin, carbamazepine
Photosensitivity	Phenobarbitone, valproic acid, carbamazepine
Erythema multiforme	Valproic acid, phenobarbital
Hair curling	Valproic acid

CADRs by AEDs increase in presence of certain risk factors such as female sex, geriatric age group, polypharmacy and hepatorenal comorbidities (Box 36.2). Levels of phenytoin, carbamazepine, phenobarbital and lamotrigine, which are metabolized through hepatic route, will increase in conditions with hepatic damage. Inappropriate prescribing, medication errors, self-medication, over-the-counter (OTC) use and ignoring history of allergy may be the responsible factors in an Indian setting.[6]

Box 36.2: Risk factors for cutaneous adverse drug reactions

- Female sex
- Increasing age
- Polypharmacy
- Comorbidities (hepatic and renal)
- Multiple AEDs
- Immunosuppressed patients
- Autoimmune disorders

PATHOGENESIS

Pathophysiology varies for different CADR patterns due to AEDs. Various mechanisms involved are gene polymorphisms, detoxification capacity of keratinocytes, deficiency of epoxide hydrolase detoxifying enzyme system, exaggerated T-cell idiosyncratic response and upregulation of apoptotic pathways. The reaction pattern may be due to excessive drug level–induced toxicity, metabolic idiosyncrasy due to locally formed reactive metabolites and immunological idiosyncrasy due to neoantigen formation to intermediate metabolites. Variation in the regulation and expression of the human cytochrome P450 enzyme system may play a key role in both interindividual variation in sensitivity to drug toxicity and tissue-specific damage. Carbamazepine is metabolized to reactive oxidative intermediate 10,11-epoxide by cytochrome P3A4, which is further detoxified by epoxide hydrolase to carbamazepine-10,11-diol. Genetic polymorphisms resulting in increased ADRs by AEDs may be due to distinct DNA mutations in cytochrome enzyme system (CYP2C19: Phenytoin, carbamazepine and phenobarbital), deficient detoxification by epoxide hydrolases of aromatic amines (phenytoin, carbamazepine, and phenobarbital) and upregulation of Fas/FasL on keratinocytes. Various mechanisms are involved in target damage to the cells as given in Table 36.4.[7]

Certain specific human leukocyte antigen (HLA) genotypes have been implicated in TEN caused by carbamazepine, namely HLA-B*1502 (in Han Chinese/Indian population) and HLA-A*3101(North Europeans).[8] People with deficient detoxification of intermediary drug metabolites such as epoxide from carbamazepine, 10-monohydroxyl from oxcarbazepine, phenobarbital from primidone may act as haptens providing antigenic stimulus to develop TEN. It is an immune-mediated, HLA class I–restricted drug hypersensitivity reaction. There is clonal expansion of cytotoxic CD8+ T cells and along with the help of perforins, granzyme B, granulysins and tumor necrosis factor-α (TNF-α) mediate the keratinocyte apoptosis leading to epidermal necrosis. TNF-α upregulates Fas (death receptors) on effector cells and Fas ligand (FasL) on the keratinocytes leading to upregulation of apoptotic pathway.[9,10] In AGEP, it is postulated that keratinolytic cytokines such as perforins, granzymes and FasL, all produced by the drug-specific CD4+ T cells infiltrating epidermis, are responsible for the vesiculation. These cells further express interleukin-8 (IL-8), which leads to neutrophil chemotaxis and causes pustule formation. Keratinocyte apoptosis and the inflammatory reaction are also induced by protein kinase activation through independent signaling pathways.[11,12]

Table 36.4: Pathophysiology of cellular damage by antiepileptic drugs

Molecular target	Mechanism	Cells involved	Drug reaction pattern
Slow acetylation	Deficient detoxification	CD8+ T cells	TEN/SJS, DRESS
Slow acetylation	Deficient detoxification	CD4+ T cells, eosinophils, reactivation of HHV-6, HHV-7, EBV, CMV	DRESS
Neoantigen formation	Apoptosis (CD8 activation)	Fas/FasL on keratinocytes	SJS/TEN
Neoantigen formation	Induce antibody	Neutrophils	AGEP, vasculitis
Independent signaling pathways	Keratinocyte apoptosis	Activation of protein kinases	AGEP

TEN - toxic epidermal necrolysis; SJS - Stevens–Johnson syndrome; DRESS - drug reaction with eosinophilia and systemic symptoms; AGEP - acute generalized exanthematous pustulosis; HHV-6 and HHV-7 - human herpesvirus-6 and 7; EBV - Epstein–Barr virus; CMV - cytomegalovirus.

In drug hypersensitivity syndrome, there is a genetic deficiency of detoxifying enzymes of aromatic amine AEDs leading to an accumulation of drug metabolites. The metabolites covalently bind to cell macromolecules causing cell death or inducing secondary immunological response. Drug-specific T cells release IL-5, which causes eosinophilic chemotaxis and its subsequent inflammatory cascade response. Drug-specific T cells have been isolated from the blood and skin of patients in whom DRESS syndrome was induced by lamotrigine and carbamazepine. Sequential reactivations of several herpesviruses [human herpesvirus-6 (HHV-6), human herpesvirus-7 (HHV-7), Epstein–Barr virus (EBV), and cytomegalovirus (CMV)] can be detected coincident with the clinical symptoms of drug hypersensitivity reactions. In drug-induced vasculitis, antibodies that are formed against the drugs (hapten) act on the vascular endothelium and vascular wall leading to vasculitis.[13–15]

DRUG INTERACTIONS

Major risk factor for CADRs is the drug interaction. When multiple-drug therapy is used, there is a possibility of clinically relevant drug interactions, which in patients with epilepsy are particularly common for a variety of reasons as mentioned in Table 36.5.[16]

Table 36.5: Reasons for frequent drug interactions in patients on anti epileptic drugs

No.	Factors
1	AEDs are administered for prolonged periods, often for a lifetime, thereby increasing the probability of co-prescription.
2	Most AEDs have a narrow therapeutic index, and even relatively modest alterations, in their pharmacokinetics can result in loss of response or toxic effects.
3	Most widely used AEDs (carbamazepine, valproic acid, phenytoin, and phenobarbital) have prominent effects on the activity of enzymes that metabolize the majority of existing medication.
4	Most of the old and new-generation AEDs are substrates of the same enzymes.

AED - antiepileptic drug.

Some patients with difficult-to-treat epilepsy benefit from combination therapy with two or more AEDs. In these situations, clinically important drug interactions may occur. Cross-reactivity with carbamazepine is observed with phenytoin, phenobarbital, lamotrigine, and oxcarbazepine. Valproic acid inhibits lamotrigine glucuronidation, thereby increasing its plasma concentration and toxicity. Valproate is an epoxide hydrolase enzyme inhibitor. Patients comedicated with lamotrigine, carbamazepine, phenobarbital and newer AEDs, including felbamate, rufinamide and stiripentol should be given at reduced dosages (by up to 80%) to avoid adverse effects. Zonisamide is related to sulfonamide and should not be combined with sulfa drugs.[17] Cytochrome P3A4 inducers such as macrolide antibiotics, isoniazid, calcium channel blockers, and azoles can increase the levels of carbamazepine and precipitate toxicity.[18] Though not standardized, therapeutic drug monitoring (TDM) of newer AED combinations with lamotrigine, levetiracetam, tiagabine, felbamate, gabapentin, oxcarbazepine, topiramate, vigabatrin and zonisamide will help in better efficacy and minimizing drug toxicity.[19]

CLINICAL FEATURES

Summary of individual AED reaction patterns and individual adverse skin reactions to antiepileptics is given in Tables 36.6 and 36.7. The spectrum of clinical and histological reaction patterns induced by AED is shown through Figs. 36.1 to 36.10.

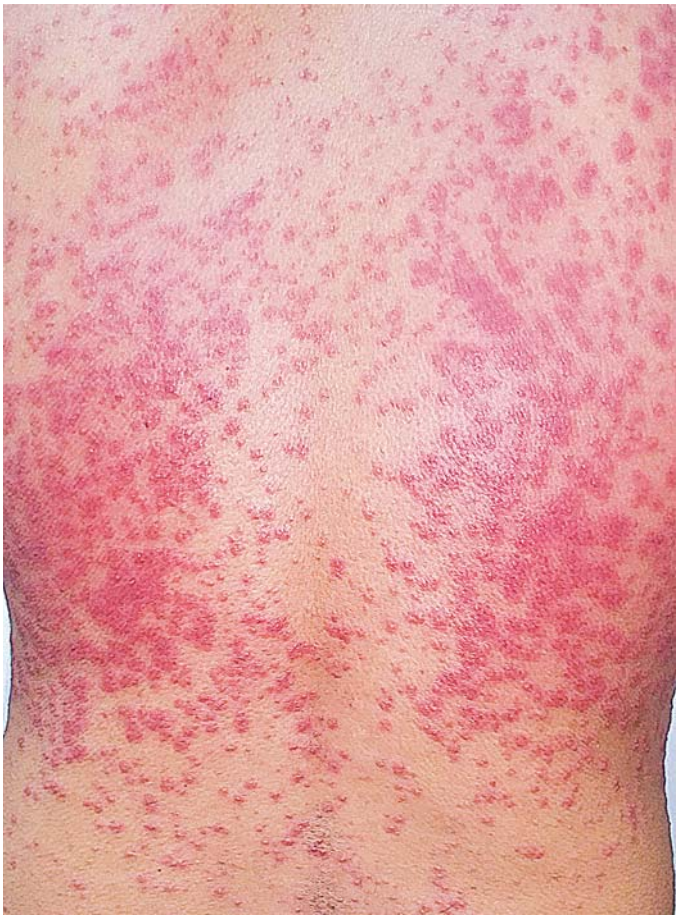

Fig. 36.1: Maculopapular rash due to carbamazepine.

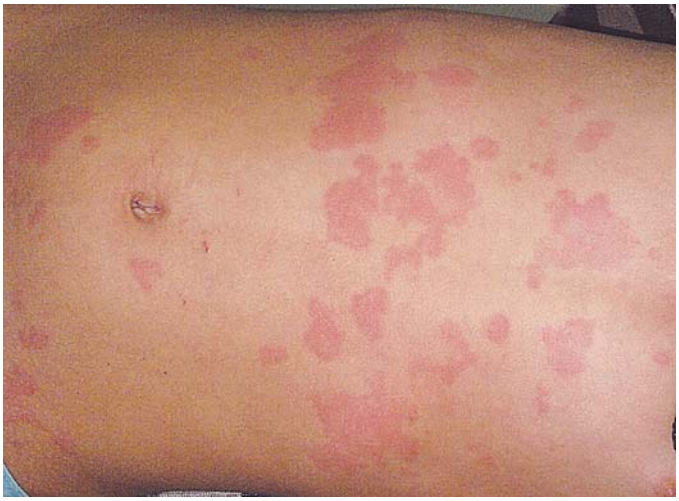

Fig. 36.2: Urticarial rash in a child due to phenobarbitone.

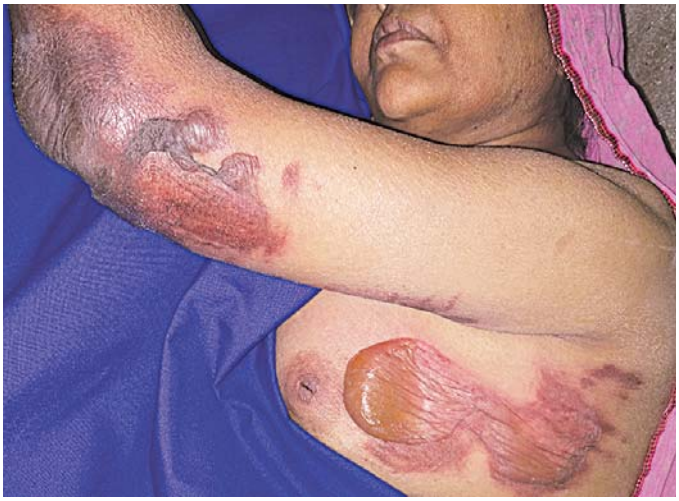

Fig. 36.3: Bullous fixed drug eruption in a female patient taking carbamazepine for trigeminal neuralgia.

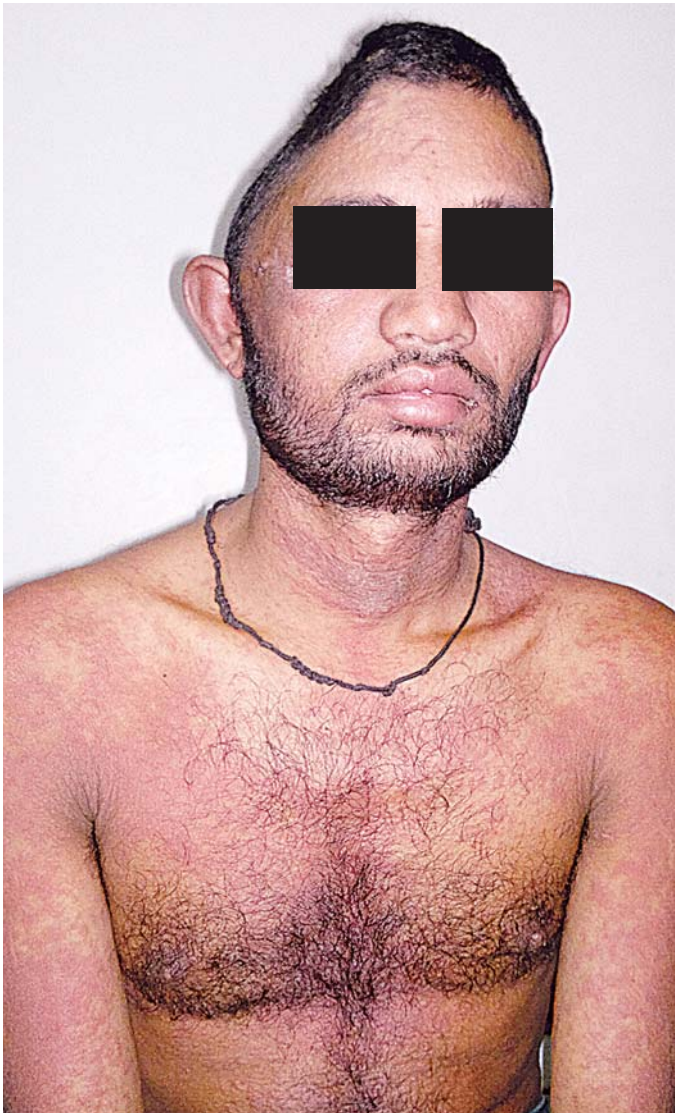

Fig. 36.4: Drug induced hypersensitivity to phenytoin in a young boy who had undergone brain surgery.

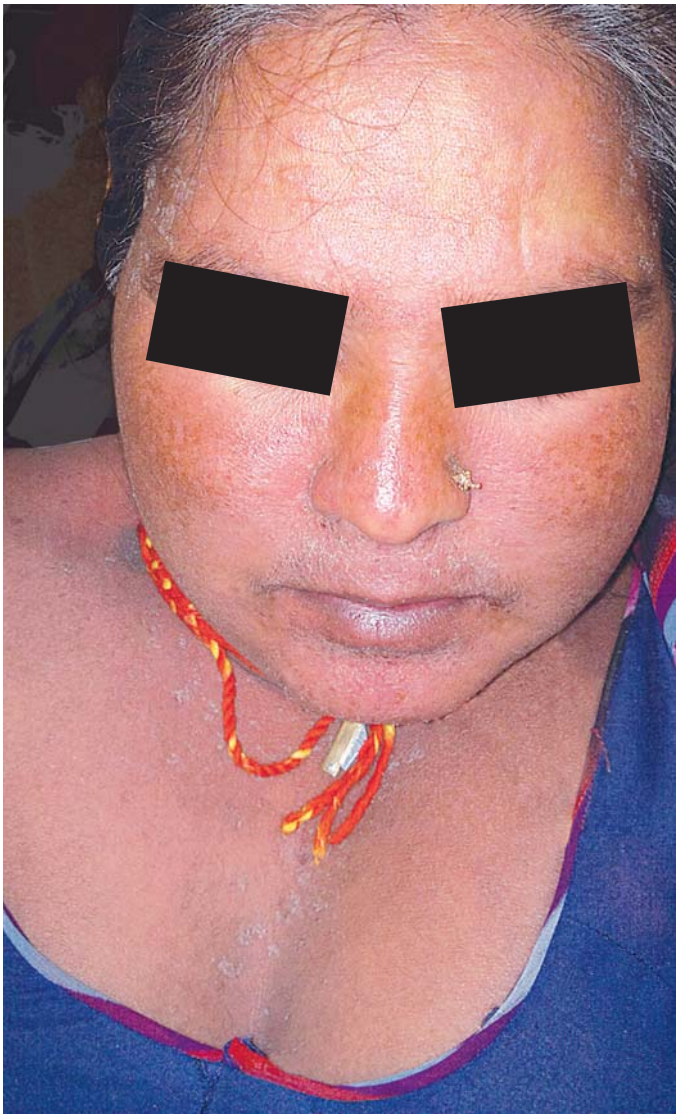

Fig. 36.5: Drug induced hypersensitivity to sodium valproate in a patient of generalized seizures.

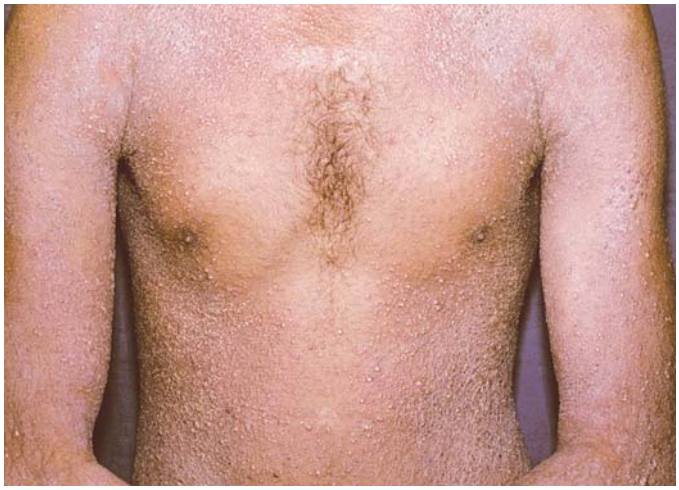

Fig. 36.6: Pustular drug rash (AGEP) in a patient taking carbamazepine (Courtesy of Dr. M. Ramam, New Delhi).

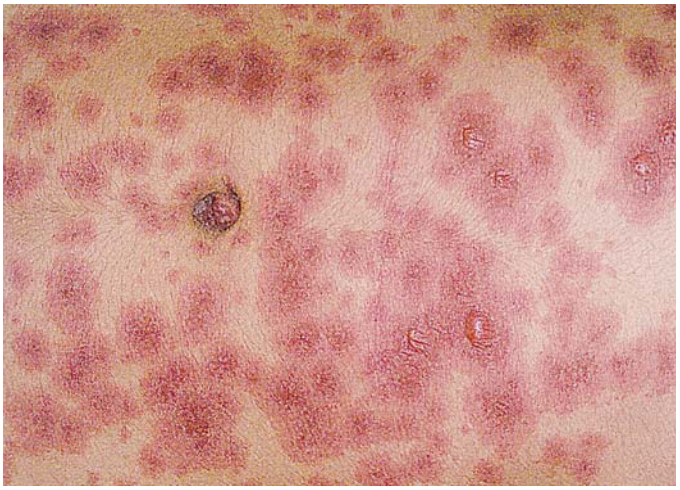

Fig. 36.7: SJS in a patient on lamotrigine.

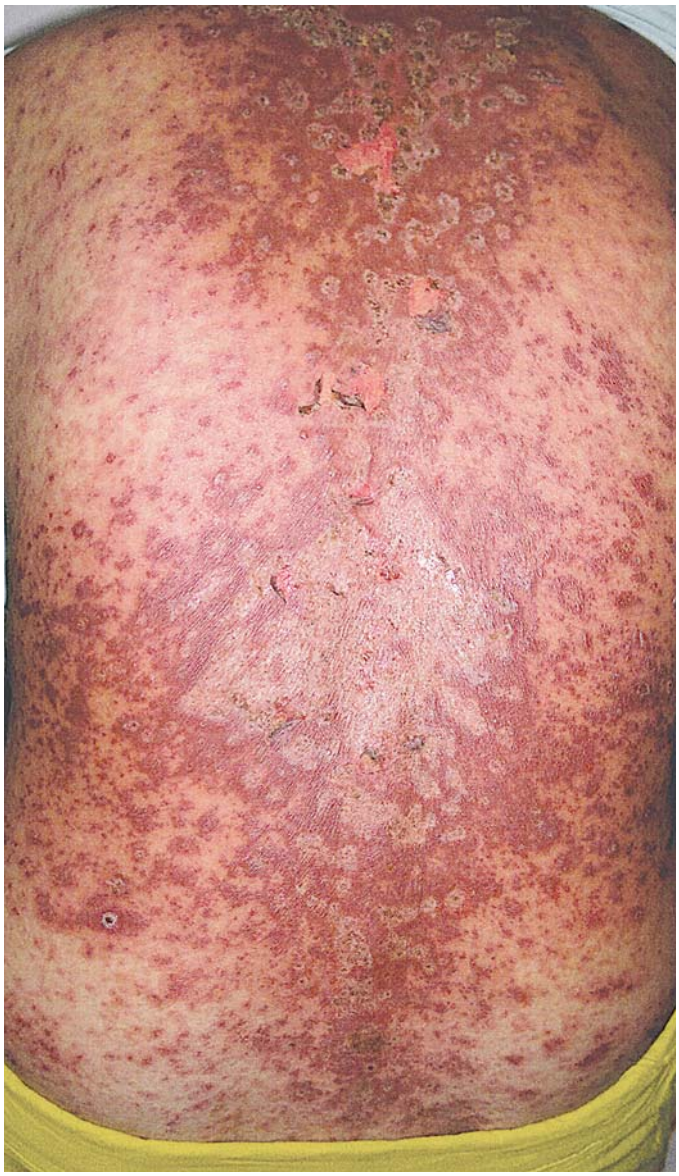

Fig. 36.8: SJS/TEN overlap in a patient taking phenytoin.

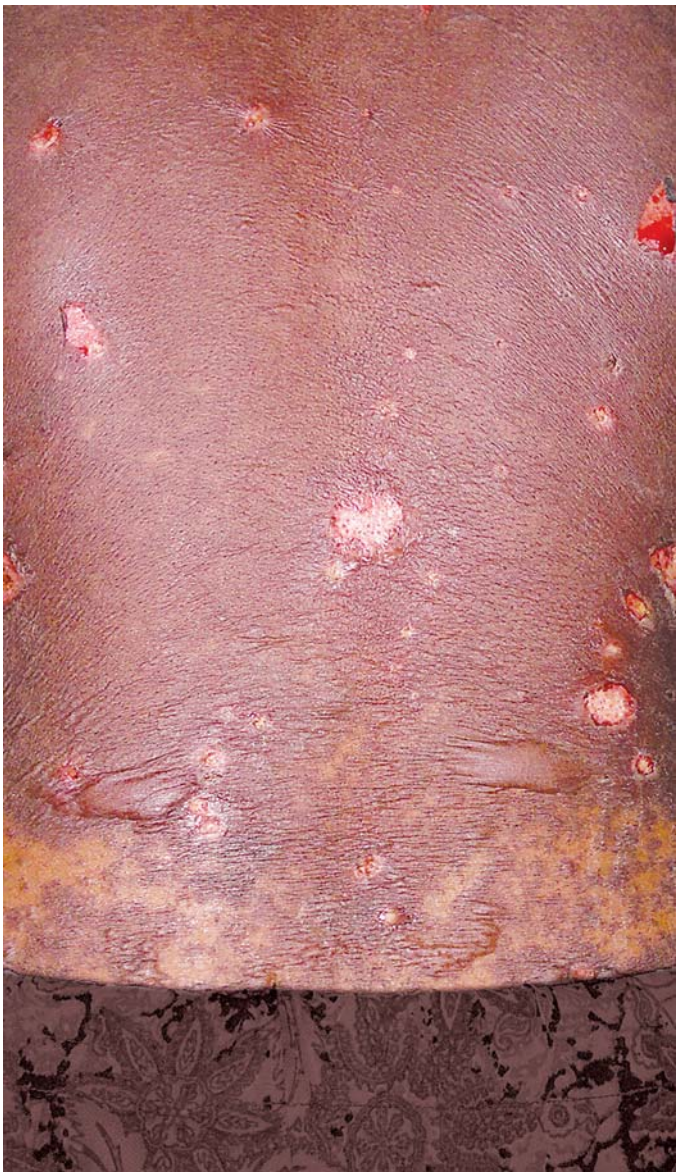

Fig. 36.9: TEN in patients on carbamazepine.

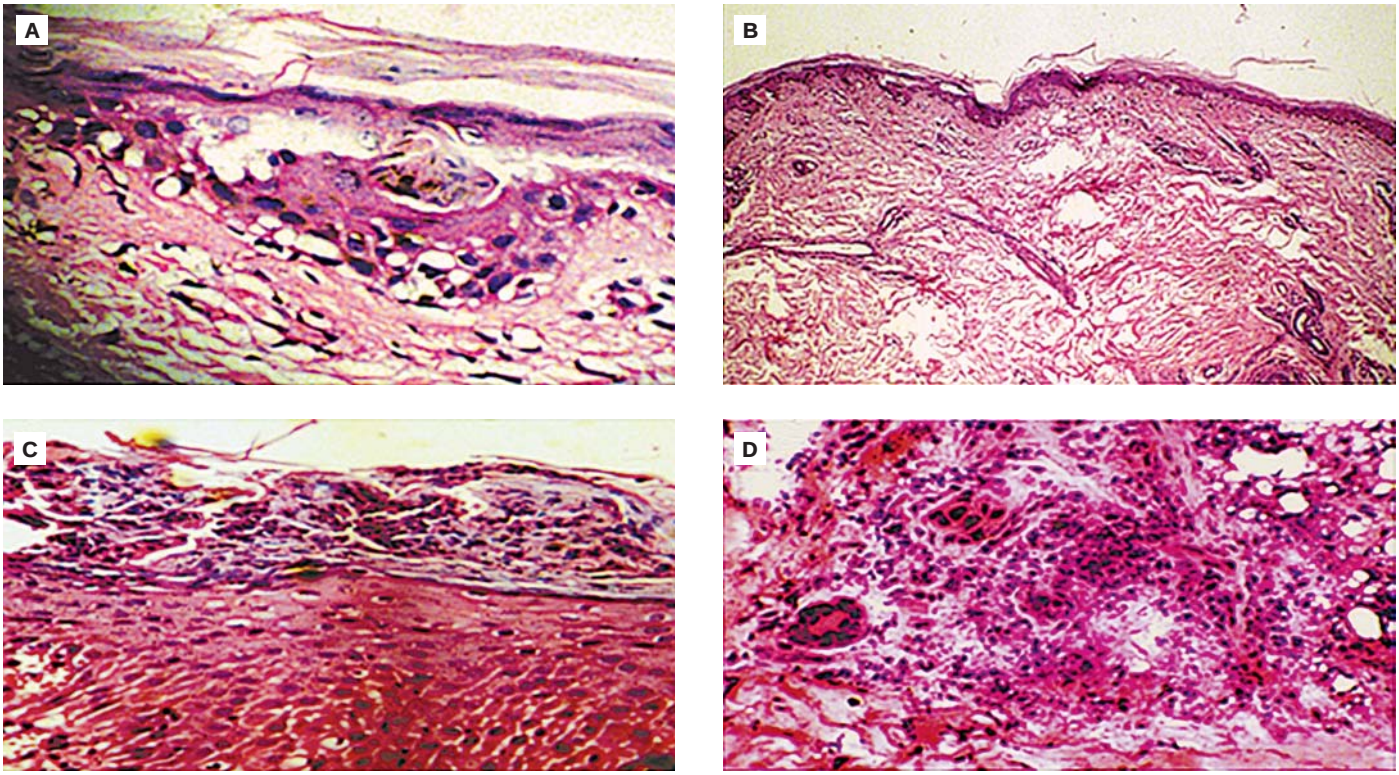

Fig. 36.10: Histopathological features of (A) Toxic epidermal necrolysis (TEN) showing basal cell vacuolization and satellite cell necrosis (H&E, 40×); (B) Erythroderma showing perivascular lymphocytic infiltrate (H&E, 10×); (C) AGEP showing subcorneal necrosis with neutrophils (H&E, 40×); (D) Vasculitis showing infiltration and vessel wall damage (H&E, 40×).

TEN (Lyell's syndrome) is a rare, severe, life-threatening idiosyncratic exfoliative disease involving skin and mucosa. Common AEDs causing SJS/TEN are given in Box 36.3.

Box 36.3: Antiepileptic drugs causing Stevens–Johnson syndrome/toxic epidermal necrolysis

- Carbamazepine
- Phenytoin
- Phenobarbital
- Lamotrigine
- Zonisamide
- Oxcarbazepine

Drug-induced erythroderma is characterized by widespread, generalized erythema and desquamation extending to >90% of body surface area (BSA). Compared to other causes of erythroderma, the drug-induced cases are sudden in onset, rapidly progressive and resolve faster. Extensive exfoliation of the skin is seen in erythroderma.

DRESS, also called drug hypersensitivity syndrome (DHS) or drug-induced delayed multiorgan hypersensitivity syndrome (DIDMOHS), is another severe idiosyncratic drug reaction associated with multiorgan involvement. A characteristic triad of fever, rash and internal organ involvement is considered diagnostic. The symptoms develop 2–6 weeks after intake of drug. Antiepileptic medications, such as phenytoin and phenobarbital, are thought to be the predominant causes of DRESS syndrome with an incidence of 1 case per 5,000–10,000 exposures.[20] Mortality is about 10%.[21,22] Drugs implicated in DRESS are given in Box 36.4. AEDs mentioned in Box 36.5 can cause DRESS, SSLRs, and pseudolymphomas. Differentiating features are given in Table 36.6.

Box 36.4: Antiepileptic drugs causing drug reaction with eosinophilia and systemic symptom

- Carbamazepine
- Phenytoin
- Phenobarbital
- Lamotrigine
- Oxcarbazepine
- Primidone
- Zonisamide

Box 36.5: Antiepileptic drugs causing pseudolymphoma

- Carbamazepine
- Phenytoin
- Lamotrigine
- Phenobarbital
- Valproic acid

Table 36.6: Difference between drug hypersensitivity syndrome, pseudolymphoma, and serum sickness–like reactions

Syndrome	Cutaneous features	Onset	Fever	System involvement	Arthralgia	Lymphadenopathy
DHS	Exanthem Exfoliative dermatitis	2–6 weeks	Present	Present	Absent	Present
Pseudolymphoma	Papules and nodules	6 months	Absent	Absent	Absent	Present
SSLR	Urticaria Exanthem	7–14 days	Present	Absent	Present	Present

DHS - drug hypersensitivity syndrome; SSLR - serum sickness–like reaction.

APPROACH TO A PATIENT WITH CADRs TO AEDs

Types of cutaneous manifestations by AEDs and the reaction pattern by individual AEDs are summarized in Tables 36.7 and 36.8. Diagnosis and workup of drug reactions by AEDs[6,7] are summarized in Tables 36.9 and 36.10.

Table 36.7: Summary: types of skin reactions to anticonvulsant drugs

Reaction	Comments
Morbilliform Carbamazepine Phenytoin Phenobarbital Lamotrigine Zonisamide Oxcarbazepine	• Widespread • erythematous maculopapular rash • Itching • May progress to erythroderma • Usually resolves rapidly on withdrawal of the drug
Urticarial drug eruption Carbamazepine Phenytoin Phenobarbital Lamotrigine	• Transient wheals with pale centers and red borders • Migratory pattern, polycyclic, recurrent • Anaphylaxis may occur with subsequent administration of the drug
SJS/TEN Carbamazepine Phenytoin Phenobarbital Lamotrigine Zonisamide Oxcarbazepine	• Usually develops within the first week of taking the drug • Serious and potentially fatal skin reaction with purpuric lesions and sheet-like skin loss • Mucous membrane involved • Apoptosis, CD8+ cells

(Continued...)

Table 36.7: Summary: types of skin reactions to anticonvulsant drugs

Reaction	Comments
Drug hypersensitivity syndrome Carbamazepine Phenytoin Phenobarbital Lamotrigine Oxcarbazepine Primidone Zonisamide	• Symptoms usually develop 2–6 weeks • Symptoms include the triad of fever, generalized maculopapular rash, and lymphadenopathy • Can involve internal organs such as the kidneys, liver, central nervous system, and bone marrow • T cells, eosinophils, reactivation of herpesviruses • Diagnosis: RegiSCAR criteria • Lymphocyte blast transformation test
Pseudolymphoma Carbamazepine Phenytoin Lamotrigine Phenobarbital Valproic acid	• Onset 6 months • Papules and nodules • Lymphadenopathy • No fever, arthralgia, or systemic involvement
SSLRs Carbamazepine Phenytoin Trimethadione Barbiturates Fosphenytoin	• Onset- 7–14 days • Fever • Urticarial and exanthematous rash • Arthralgia and lymphadenopathy

SJS/TEN - Stevens–Johnson syndrome/toxic epidermal necrolysis; SSLR - serum sickness–like reaction.

Table 36.8: Antiepileptic drugs causing cutaneous adverse reactions

Drug	Skin reaction
Carbamazepine	• Drug hypersensitivity • Urticaria • SJS/TEN • Photosensitivity • Fixed drug eruption • LE-like syndrome • Morbilliform eruptions • Vasculitis
Phenytoin	• Erythroderma • Facial pustules • Hyperpigmentation • Hypertrichosis • Lupus-like symptoms • Drug hypersensitivity syndrome
Fosphenytoin	• Bullous rash • Exfoliative dermatitis • Pruritus • Gingival hyperplasia • Lupus-like symptoms • Erythema multiforme
Phenobarbital	• Morbilliform rash • Urticaria • Erythema multiforme • Photosensitivity • Acneiform (acne-like) rash • Purpura
Lamotrigine	• Morbilliform rash (in 10%) • Angioedema • Pruritus • SJS/TEN • Anticonvulsant hypersensitivity syndrome
Valproic acid	• Diaphoresis • Erythema multiforme • Transient alopecia • Petechiae • Photosensitivity • Pruritus

SJS/TEN - Stevens–Johnson syndrome/toxic epidermal necrolysis; LE-like syndrome - lupus erythematosus–like symptom.

Table 36.9: Diagnosis of drug reactions

Definite	a) Reasonable temporal sequence after a drug level has been established in body fluids. b) Recognized response to the offending drug. c) Improvement after drug withdrawal. d) Reaction reappears on reexposure.
Probable	As in (a) and (c) but not confirmed by rechallenge of the drug.
Possible	As in (a) but involves an unpredictable reaction explained by the patient's condition.

Table 36.10 Workup of antiepileptic drug–induced drug reactions

1	Detailed history (reactions can occur within 24–48 hours to 6–8 weeks)
2	Polypharmacy (combination AEDs and drugs for comorbid conditions)
3	Drug interactions (enzyme inhibitors increase blood level of valproate, interaction of aromatic amines with AEDs)
4	Comorbid conditions (hepatic metabolism: Phenytoin, carbamazepine, phenobarbital, oxcarbazepine; renal metabolism: Gabapentin, levetiracetam topiramate)
5	History of drugs
6	Skin tests a) Oral provocation in fixed drug eruption b) Open topical test: Suspected drug applied with 10% petrolatum over eruption and over normal skin. Positive results are observed as erythema after 24 hours, e.g. barbiturates and carbamazepine c) Patch tests: Use 30% concentration of the offending drug in DRESS
7	Lymphocyte transformation test, which measures proliferation of T lymphocytes in vitro, if done within a week of appearance of rash, is a reliable technique to demonstrate the causative agent in DRESS
8	Histopathology
9	HLA screening for carbamazepine: HLA-B*1502, HLA-A*3101 allele

AED - antiepileptic drug; DRESS - drug reaction with eosinophilia and systemic symptoms; HLA - human leukocyte antigen.

PREVENTION[23]

CADRs can be prevented to a certain extent by using modified Schumock and Thornton criteria as mentioned in Table 36.11.

Table 36.11: Modified Schumock and Thornton criteria (one or more)

Definitely preventable
• History of allergy or previous reaction to the drug
• Inappropriate selection of drug in relation to the diagnosis and characteristics of the patient
• Documentation of toxic serum drug concentration
• Presence of a known treatment for the ADR
Probably preventable
• Lack of required therapeutic drug monitoring
• Involvement of drug interaction
• Involvement of poor compliance and lack of preventable measures causing ADR

ADR - adverse drug reaction.

CONCLUSION

In conclusion, prompt diagnosis, immediate withdrawal of incriminated drug, early referral to a specialized center, aggressive management, good supportive care with fluid and nutritional support, multidisciplinary team work and control of infection are crucial in minimizing the morbidity and rate of mortality. Avoidance of specific AEDs in population at risk, appropriate dose titration and monitoring of clinical and laboratory parameters can minimize the occurrence of idiosyncratic responses.

LEARNING ESSENTIALS

- Antiepileptic drugs (AEDs) are one of the most commonly prescribed drugs causing adverse cutaneous drug reactions.
- The spectrum of cutaneous adverse drug reactions (CADRs) due to AEDs ranges from a transient maculopapular rash to life-threatening conditions such as drug reaction with eosinophilia and systemic symptom (DRESS) and toxic epidermal necrolysis (TEN).
- Aromatic anticonvulsants (phenytoin, phenobarbitone, carbamazepine and lamotrigine) are the most commonly implicated drugs, but newer AEDs (oxcarbazepine, felbamate, primidone and zonisamide) have also been implicated in serious CADRs.
- Early identification and stoppage of the offending drug as soon as possible is of utmost importance in a case of CADR.
- A knowledge about the individual drug reaction pattern of AEDs is useful in early identification of a CADR and will help the treating physician immensely in predicting the prognosis of the ADR.
- Drug interactions form a major risk factor developing CADRs. Therefore, caution should be taken while prescribing combination of AEDs.
- Age of the patient, other comorbidities, immune status of the patient and presence of autoimmune diseases should be taken into consideration while prescribing combination of AEDs.
- Avoidance of specific AEDs in population at risk, appropriate dose titration and monitoring of clinical and laboratory parameters can minimize the occurrence of idiosyncratic responses.
- Screening for specific human leukocyte antigen (HLA) genotypes can be used in prevention of CADRs such as TEN where facilities are available.

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Chapter

37

Purpuric Drug Rash and Cutaneous Adverse Drug Reactions to Anticoagulants

Rajiv Sridharan • Asokan Neelakandan

SUMMARY

- Purpura is mucocutaneous hemorrhage and encompasses a variety of morphological and etiological subsets.
- Drug induced purpura can be intravascular, vascular, or extravascular.
- The clinical presentation of drug induced purpura is often indistinguishable from their non-iatrogenic counterparts and varies from pinpoint lesions to ecchymosis and retiform purpura.
- Anticoagulants and non steroidal anti-inflammatory agents are the common drugs causing purpura.
- Laboratory findings may be helpful in some cases, such as in drug induced thrombocytopenia or purpura due to specific antibody formation.

INTRODUCTION

Purpura is discoloration of the skin or mucous membranes due to extravasation of the red blood cells. It can be classified on the basis of morphology or etiology, but no single approach is satisfactory. The various morphologic subsets of purpura are (1) macular purpura that can be subdivided on the basis of size into (i) petechiae ≤4 mm, (ii) intermediate macular 5–9 mm, and (iii) ecchymosis ≥1 cm; (2) palpable purpura, and (3) retiform purpura that can be (i) inflammatory and (ii) noninflammatory.

CLASSIFICATION

Broadly, purpuric drug rash can be caused by intravascular, vascular, or extravascular factors. The etiologic classification of purpuric drug rash is illustrated in Fig. 37.1. The clinical spectrum of purpuric drug rash is represented in Figs. 37.2-9.

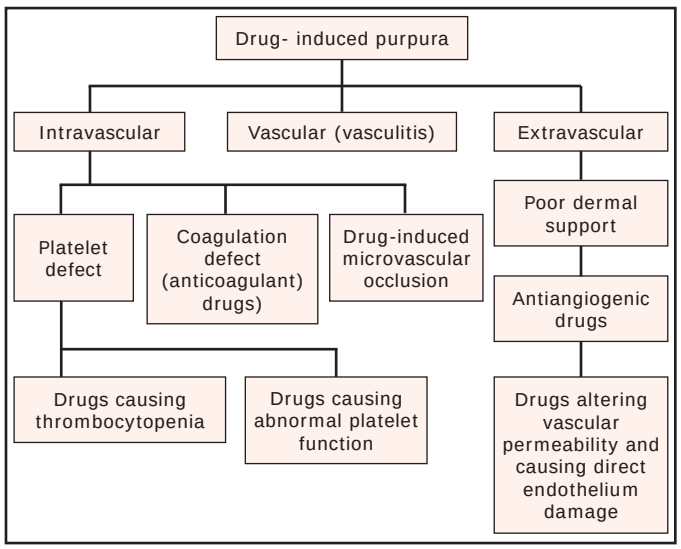

Fig. 37.1: Etiological classification of purpuric drug rash.

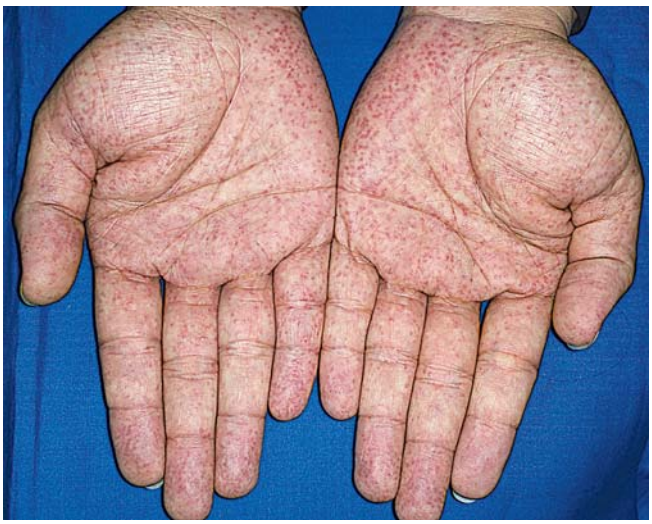

Fig. 37.2: Purpuric rash on palms in a patient on chloroquine.

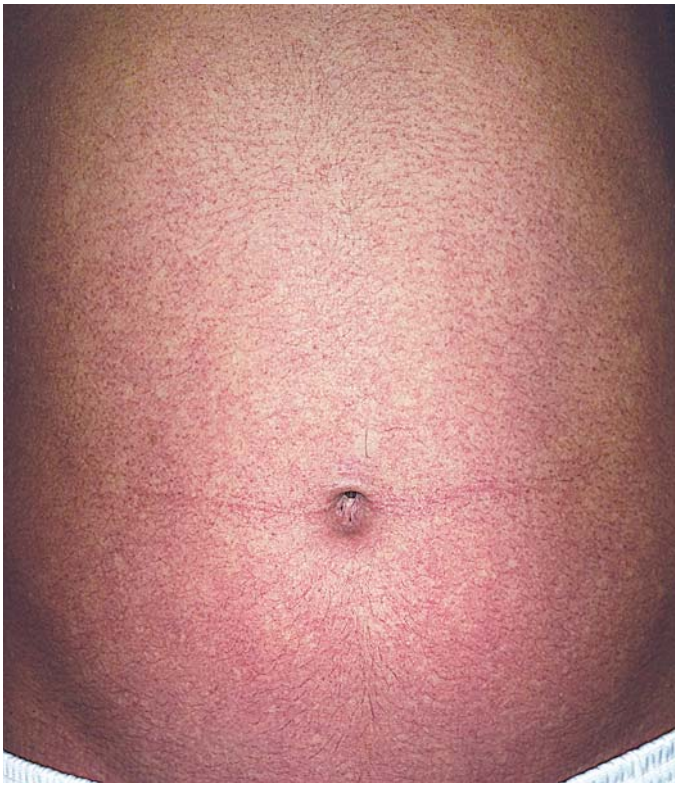

Fig. 37.3: Thrombocytopenic purpuric drug rash to quinine.

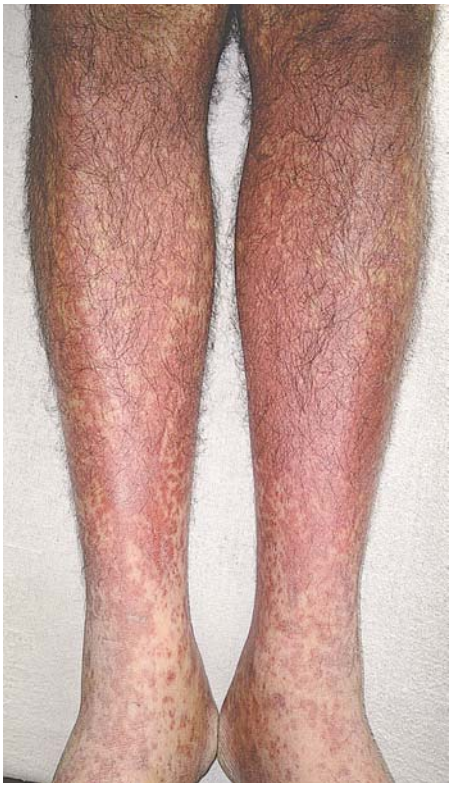

Fig. 37.4: Purpuric drug rash in a patient on carbamazepine.

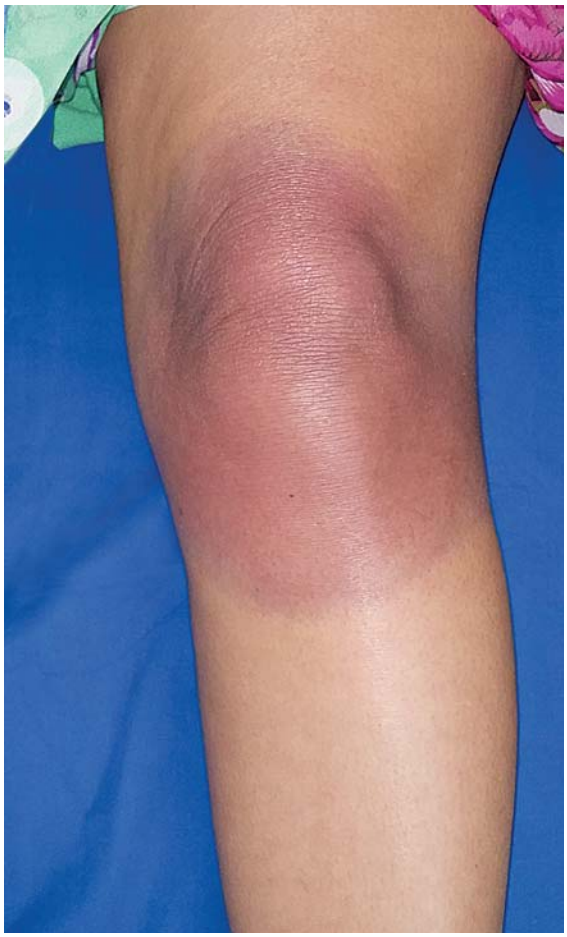

Fig. 37.5: Ecchymoses in a patient on aspirin.

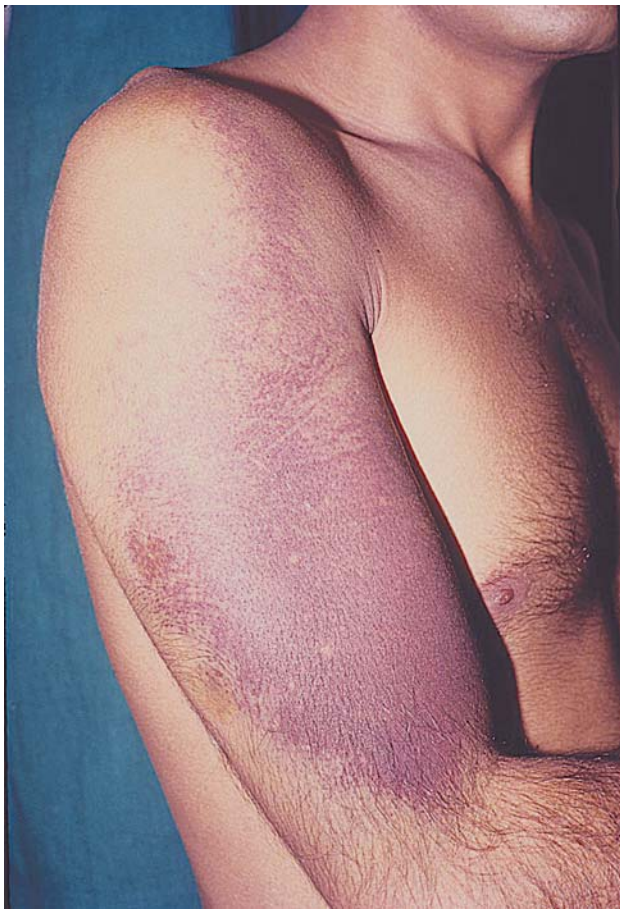

Fig. 37.6: Purpura following analgesic (Baralgan) injection. (Courtesy of Dr. M. Ramam, New Delhi.)

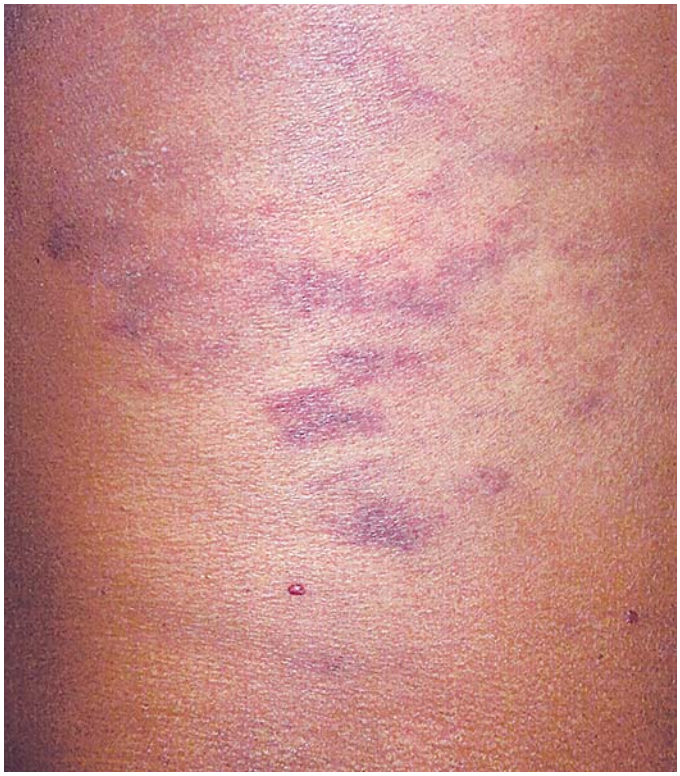

Fig. 37.7: Purpuric lesions in a patient on long term oral steroids in an elderly.

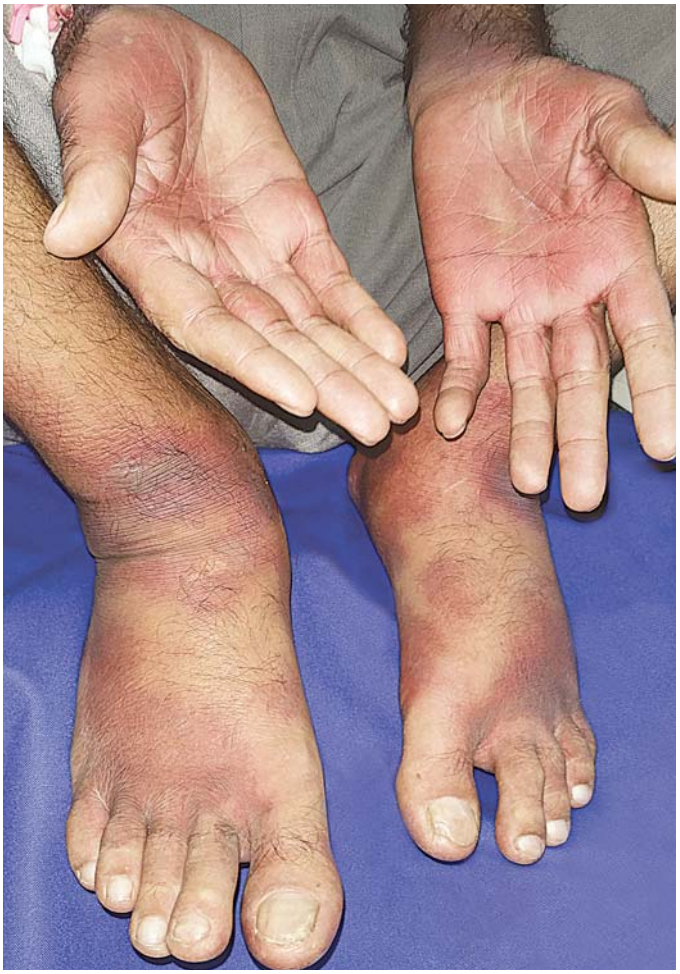

Fig. 37.8: Purpuric rash in glove and socks pattern to sulfasalazine.

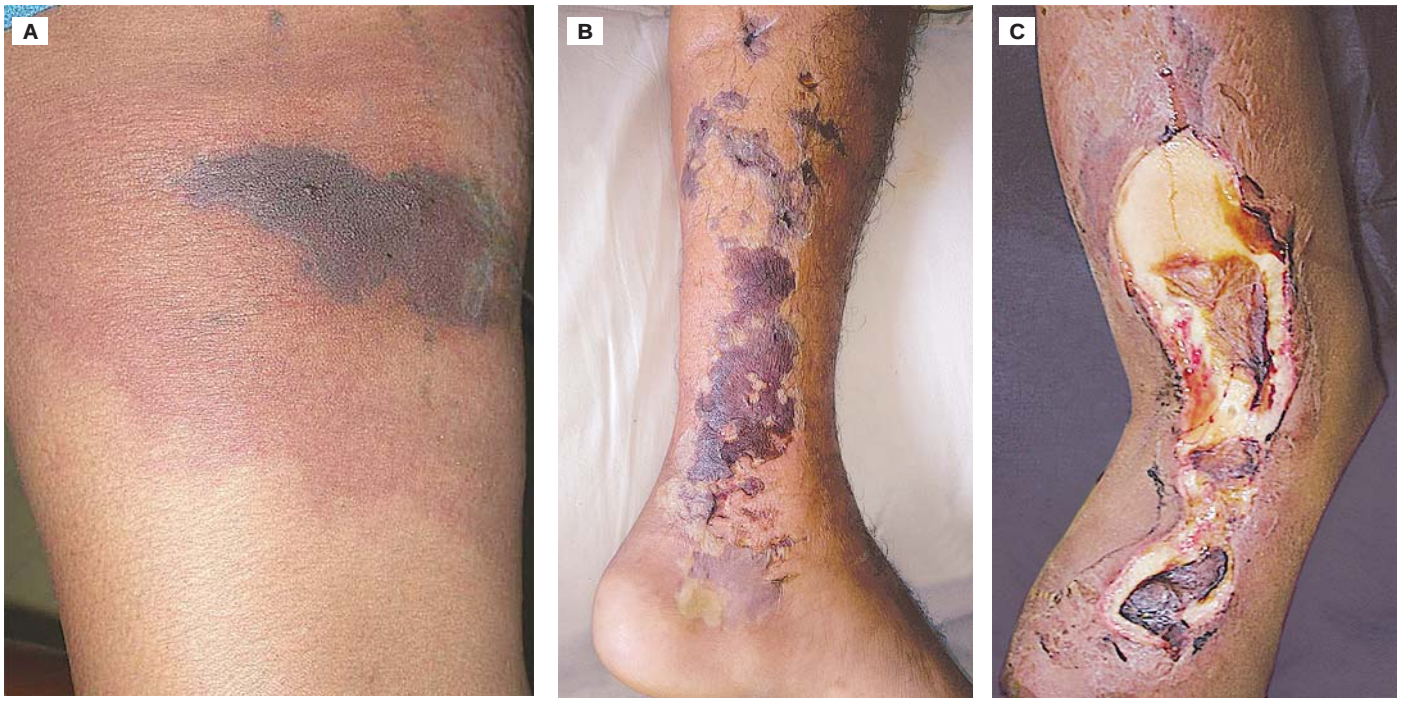

Fig. 37.9: (A–C) Warfarin induced necrosis of varying severity in patients taking warfarin for prophylaxis of deep vein thrombosis. (Figs. A & C, courtesy of Dr. Sandipan Dhar, Kolkata.)

Intravascular Causes

The intravascular causes of purpura can be due to defect in platelets, either in the form of decreased count (thrombocytopenia) or abnormal function, in coagulation or in the lumen (microvascular occlusion).

Platelet Defect

Drugs Causing Thrombocytopenia

Purpura due to platelet deficiency usually occurs with a count below 20 × 10^9/L and is seldom observed with a count above 50 × 10^9 per liter. Table 37.1 enumerates the list of drugs causing thrombocytopenia and the underlying mechanism.

Table 37.1: Drugs causing thrombocytopenia and the underlying mechanism

Mechanism		Drugs
Direct bone marrow toxicity		**Chemotherapeutic agents** (Nitrogen mustard) Benzol
Immunological bone marrow damage		Chloramphenicol
Destruction of formed platelets		
A. Immuno-logical	i. Hapten-induced antibody	**Penicillins, Heparin**
	ii. Drug-dependent (compound or conformational) antibody	**Quinine** (Figs. 37.2, 37.3) **Quinidine** NSAIDs **Anticonvulsants** {phenytoin, sodium valproate, carbamazepine (Fig. 37.4)} Antibiotics
	iii. Inhibitors of the platelet glycoprotein GIIb/IIIa	Abciximab Thiazides
B. Nonimmunological		Bleomycin

* Drugs in bold are common cause.

NSAID - nonsteroidal anti-inflammatory drug.

The onset of thrombocytopenia is usually within a week of first exposure of the drug, but can be as early as 2–3 days on re-exposure.[1] Improvement usually takes place within 10 days of stopping the offending drug; however, in some cases, such as quinine and quinidine, the duration may be too long to be explained by drug clearance or platelet lifespan and may suggest role of true antibodies.[2]

Heparin-induced thrombocytopenia is discussed in detail later in this chapter under section 'Skin Necrosis' and 'Heparin Induced Thrombocytopenia'.

Drugs Causing Abnormal Platelet Function

Drugs causing platelet dysfunction are of importance to dermatologists as patients on these medications may bleed during cosmetic procedures and skin surgeries. Causes of abnormal platelet function may overlap with causes of thrombocytopenia. Common causative drugs are enlisted in Table 37.2.

Table 37.2: Drugs causing abnormal platelet function

Drug class	Common drugs causing abnormal platelet function
Anti-inflammatory	Aspirin (Fig. 37.5) NSAIDs (Fig. 37.6)
Antibiotics	Penicillin group
Hematological	Antifibrinolytic drugs (alteplase) Fibrinolytics (streptokinase) Thienopyridines (ticlopidine and clopidogrel) Glycoprotein IIb/IIIa antagonists
Cardiovascular drugs	Nitrates Calcium channel blockers Quinidine
CNS drugs	Antidepressants Phenothiazines
Chemotherapeutic agents	Mitomycin Daunorubicin
Volume expanders	Dextran or hydroxyethyl starch
Radiocontrast media	

CNS - central nervous system; NSAID - nonsteroidal anti-inflammatory drug.

The clinical presentation of drugs causing thrombocytopenia and abnormal platelet function is same as other causes of thrombocytopenia such as immune thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulation (DIC). Although thrombocytopenia usually causes lesions upto 4 mm i.e. macular purpura, platelet dysfunction can present as macular lesions of 1 cm or greater (ecchymoses).

Coagulation Defect

Purpura and other cutaneous adverse drug reactions (CADRs) due to drugs causing coagulation defect

(anticoagulants) are discussed under section 'CADRs to Anticoagulants'.

Drugs Causing Microvascular Occlusion

Retiform purpura can develop secondary to inflammatory and non-inflammatory injury to vessels. It is imperative to distinguish between the two because they differ greatly in their approach to management. Although anti-inflammatory therapy is useful in inflammatory diseases, it may worsen occlusive diseases. The same holds true for anticoagulant therapy in vasculitides.

Drugs causing microvascular occlusion includes:

1. Heparin necrosis or heparin-induced thrombocytopenia (HIT) discussed later under section 'Skin Necrosis' and 'Heparin Induced Thrombocytopenia'.
2. Warfarin necrosis discussed later under section 'Skin Necrosis'.
3. Hydroxyurea-associated vascular necrosis.

   Hydroxyurea has been found to be associated with painful ulcers especially in perimalleolar region when instituted in patients with myeloproliferative diseases.[3,4]

Vascular Causes

Drug induced vasculitis has been described in Chapter 26.

Extravascular Causes

Poor Dermal Support

Corticosteroids causes protein degradation that leads to dermal atrophy and loss of intercellular substance, which further causes blood vessels to lose their surrounding dermal matrix, resulting in the fragility of dermal vessels, purpuric (Fig. 37.7), hypopigmented and depressed scars.[5]

Antiangiogenic Drugs

Bevacizumab {anti-vascular endothelial growth factor (VEGF)}.

Drugs Altering Vascular Permeability or Causing Direct Endothelial Damage

There are several drugs capable of causing capillary damage. The common and important ones include acetylsalicylic acid, atropine, barbiturate, carbimazole, carbromal, chloramphenicol, chlordiazepoxide, chlorothiazide, chlorpromazine, diethylstilbestrol, furosemide, glyceryl trinitrate, gold, hair dye, indometacin, iodides, isoniazid, methyldopa, quinidine, quinine, sulfonamides, tartrazine and other food additives.

Trimethoprim–sulfamethoxazole can cause acral purpura (Fig. 37.8) resembling "gloves and socks" syndrome caused by parvovirus.[6]

Contact Purpura

Topical medications may rarely cause purpura that appears to be of irritant or toxic causation, such as clioquinol (at flexural sites), benzoyl peroxide or EMLA local anesthetic.[7,8]

Capillaritis (Pigmented Purpuric Dermatoses)

Drugs were found to be responsible for 14% of all cases of capillaritis in a large series.[9] Common causative drugs are enlisted in Table 37.3. Unlike the idiopathic form of Pigmented Purpuric Dermatoses (PPD), most of the drug-induced cases resolve within a few weeks of withdrawing the offending drug.

Table 37.3: Drugs causing capillaritis

Cardiovascular drugs	Calcium channel antagonists, β-blockers
	Angiotensin-converting enzyme inhibitors
	Nitrites
	Furosemide and other diuretics
Antihistamines	
Analgesics	Paracetamol
	Nonsteroidal anti-inflammatory agents
CNS drugs	Antidepressants
	Chlordiazepoxide
	Carbamazepine
Antibiotics	Ampicillin
	Co-trimoxazole
Others	Medroxyprogesterone acetate
	Raloxifene
	Pseudoephedrine
	Vitamin B1 derivatives
	Interferon-A
	Polyvinylpyrrolidone
	Topical 5-fluorouracil
	Glipizide
	Bezafibrate

CNS - central nervous system.

CADRs TO ANTICOAGULANTS

Anticoagulants are drugs that act on different phases of coagulation cascade and inhibit the development and progression of clot formation. They are useful in the treatment of venous thromboembolism associated with various medical conditions and surgical procedures.

Classification

Anticoagulants are broadly classified into heparins, vitamin K antagonists (coumarins), direct thrombin inhibitors and factor Xa inhibitors which are further subclassified as in Table 37.4.

Table 37.4: Classification of anticoagulants[10]

Anticoagulant class	Route of administration	Drugs
Heparins	Parenteral	Unfractionated heparin Low-molecular-weight heparins Enoxaparin Tinzaparin Dalteparin Certoparin Bemiparin Reviparin Ardeparin Heparinoids Danaparoid
Vitamin K antagonists (coumarins)	Oral	Warfarin Acenocoumarol Phenindione
Direct thrombin inhibitors	Parenteral	Hirudin Lepirudin Phenindione Desirudin Argatroban
	Oral	Dabigatran Melagatran Ximelagatran
Factor Xa inhibitors	Parenteral	Synthetic pentasaccharides Fondaparinux Idraparinux
	Oral	Direct factor Xa inhibitors Rivaroxaban Apixaban Betrixaban Edoxaban

Cutaneous Adverse Drug Reactions to Anticoagulants

Various adverse drug reactions to parenteral as well as oral anticoagulants (OACs) are shown in Box 37.1.

Box 37.1: Adverse drug reactions to parenteral and oral anticoagulants

- Heparin-induced hypersensitivity reaction
- Skin necrosis
  - Heparin induced
  - Warfarin induced
- Heparin-induced thrombocytopenia
- Bullous hemorrhagic dermatoses
- Pyoderma gangrenosum–like lesions
- Hemorrhagic purpura due to heparin
- Warfarin-induced calciphylaxis
- DRESS syndrome
- Maculopapular rashes
- Leukocytoclastic vasculitis
- AGEP

DRESS - drug rash with eosinophilia and systemic symptoms; AGEP - acute generalized exanthematous pustulosis.

Heparin-Induced Hypersensitivity Reaction

Both delayed and immediate hypersensitivity reactions can occur with heparin. Immediate hypersensitivity reactions may present as urticaria.[11] It can sometimes result even in anaphylaxis. Delayed hypersensitivity reactions presenting as localized or generalized dermatitis are more common than immediate hypersensitivity reactions.[12] Progression to generalized exanthematous rash, though possible, is rare. Both unfractionated heparin and low-molecular-weight heparins can induce hypersensitivity reactions. Risk for cross-reactions after a cutaneous delayed-type hypersensitivity (DTH) reaction to heparin preparations is independent of their molecular weight.[13–15] The low-molecular-weight heparin, enoxaparin, is a particularly frequent cause. DTH to heparin can also present as inflammatory plaques at injection sites or as erythematous, well-circumscribed lesions without necrosis.[11]

One study reported a prevalence of 7.5% of delayed hypersensitivity reactions in patients on heparin.[16] Interestingly, none of these patients developed heparin necrosis which is another characteristic adverse reaction to heparin. Substituting one type of heparin preparation with another one is only occasionally helpful in preventing the reaction as there is a definite chance of cross reactions.[14] Several substitutes of heparin such as danaparoid have shown delayed hypersensitivity on skin tests.[17]

The lowest overall risk for cross-reactions is with fondaparinux and pentosan polysulfate. [12,15] Some physicians recommend fondaparinux as the best alternative when a DTH reaction occurs.[15] Dabigatran also is a comparatively safer alternative.[18] Hirudins also can be good alternative in many patients as it has an entirely different chemical structure.[19] Occasionally, patients may show positive skin reaction to hirudin too.

Interestingly, change of route of administration from subcutaneous to intravenous can prevent further hypersensitivity reactions in many patients.[20,21] Desensitization protocols have been developed to induce tolerance to warfarin.[22] Some physicians have also suggested acid citrate dextrose extracorporeal photopheresis as an alternative treatment option for patients with heparin allergy.[23]

Skin Necrosis

Skin necrosis is a very remarkable and often alarming complication of treatment with anticoagulants. It usually begins shortly after initiation of therapy, generally between the third and the sixth day of treatment. It may occur not only at the site of injection, but also at distant sites. It is thought to be due to a transient hypercoagulable state in patients with protein C deficiency or in rare cases, protein S deficiency. Though originally reported with use of heparin,[24–26] later several anticoagulants were shown capable of producing such lesions.[27–31] Sometimes it can occur late in therapy, as late as 2 years after starting treatment.[32]

Heparin-induced skin necrosis is one of the symptoms of immune-mediated heparin-induced thrombocytopenia and should result in the immediate cessation of heparin therapy to prevent potentially fatal thrombotic events. This is in contrast to coumarin-induced skin necrosis, where therapy may be continued or restarted at a lower dose.[15] Classic skin necrosis induced by OACs is typically seen in patients with protein C and S deficiencies. Byrne et al. postulated that warfarin skin necrosis was associated with protein S deficiency and a mutation in the methylenetetrahydrofolate reductase gene.[33] Relationship between skin necrosis and thrombocytopenia is also noted.[34] Skin necrosis may be due to vasculitis, representing a type III Arthus reaction.[11]

It was once thought that low-molecular-weight heparins may be devoid of this side effect. Subsequently several reports demonstrated that this need not be true always.[25,35] It has also been suggested that in those with warfarin necrosis, warfarin may be successfully substituted with low-molecular-weight heparin.[36] Dabigatran etexilate has been suggested as a safe anticoagulant option for preventing warfarin-induced skin necrosis in patients with protein C deficiency.[37]

The important differentiating features between heparin-induced DTH reaction, heparin-induced necrosis, and warfarin-induced necrosis are tabulated in Table 37.5.

Bullous Hemorrhagic Dermatosis

Hemorrhagic bullae are another side effect of anticoagulant therapy. It has been reported with the use of heparin[39] as well as enoxaparin.[40–42] Although the lesions are self-limited, it may take about 2–3 weeks for resolution.[42]

Recurrent Pyoderma Gangrenosum–Like Ulcers

Recurrent pyoderma gangrenosum–like ulcers may be induced by OACs.[43]

Hemorrhagic Purpura Due to Heparin

Dixit et al. described development of hemorrhagic purpura in a patient on treatment with heparin.[44]

Warfarin-Induced Calciphylaxis

Warfarin has been reported to induce calciphylaxis in a patient and this was treated with sodium thiosulphate.[45]

Drug Rash with Eosinophilia and Systemic Symptoms Syndrome

Drug rash with eosinophilia and systemic symptoms (DRESS), also named drug hypersensitivity syndrome (DHS) is an important and severe, though rare complication on treatment with anticoagulants. It has been reported mostly with fluindione.[46,47] A study published in 2012, found out 36 cases in French pharmacovigilance database since 2000.[48] One patient who developed DRESS syndrome while on treatment with acenocoumarol tolerated warfarin and dabigatran subsequently.[49]

Maculopapular Eruption

There is one case report of maculopapular rash in a patient treated with dabigatran etexilate.[50]

Leukocytoclastic Vasculitis

Leukocytoclastic vasculitis is a rare, but reported adverse effect to warfarin.[51] A review published in 2011 identified 14 such cases between 1980 and 2011.[52]

Table 37.5: Differentiating features between heparin-induced delayed type hypersensitivity reaction, heparin-induced necrosis, and warfarin-induced necrosis[10,38]

	Heparin-induced delayed type hypersensitivity reaction	Heparin-induced necrosis	Warfarin-induced necrosis
Incidence	7.5 %	Unfractionated: <3 % LMWH: <0.1 %	0.01%–0.1 %
Onset	Day 7–14 Days 1–5 [If previous sensitization (within 100 days)]	Day 5–10 Days 1–5 [If previous sensitization (within 3 months)]	Days 3–6 in 90% Almost all by day 10
Gross appearance	Inflammatory plaques at injection sites or as erythematous, well-circumscribed lesions without necrosis	Retiform purpura with minimal erythema/inflammation, may progress to necrosis at injection sites; distant sites can be involved by IV heparin.	Sudden onset pain followed by well-demarcated erythema (Figs. 37.9 A-C) that evolves to hemorrhagic bullae, necrosis, and eschar formation.
Histopathology	Perivascular lymphocytic infiltrate ± spongiosis	Vessels plugged with platelet without fibrin (white clots), necrosis, and extravasation of RBC.	Fibrin thrombi within dermal and subcuticular vessels, with no or minimal inflammation.
Associated features	Pruritus Pregnancy	Pain HITT	Pain Protein C deficiency Obesity Female sex Old age (sixth and seventh decade) Venous thromboembolism
Course	Self-limiting	Life-threatening	Self-limiting
Diagnosis	Clinical presentation, biopsy, allergy testing	Clinical presentation, platelet count and detection of antiheparin/platelet factor 4 antibodies using an enzyme immunoassay.	Clinical suspicion and biopsy
Management	Discontinue heparin	Discontinue heparin. Start heparinoid or direct thrombin inhibitor or fondaparinux.	Discontinue warfarin. Start vitamin K or protein C concentrates, FFP. Start alternative anticoagulation.
Treatment duration		4 and 12 weeks in asymptomatic patients and in those with thrombosis, respectively.	Several weeks
Ability to restart	No subcutaneous UFH or LMWH. IV heparin and fondaparinux often tolerated	No (with exception of specific surgical situations).	Yes (at low dose and slow taper), overlapping with heparin/LMWH

RBC - red blood cell; HITT - heparin-induced thrombocytopenia and thrombosis; FFP - fresh frozen plasma; UFH - unfractionated heparin; LMWH - low-molecular-weight heparin.

Acute Generalized Exanthematous Pustulosis

There has been a single case report about acute generalized exanthematous pustulosis due to anticoagulant treatment.[53]

Heparin-Induced Thrombocytopenia

HIT may occur as an isolated event without skin necrosis. Thrombocytopenia occurs in about 2% of subjects exposed to heparin, but in up to 40% after cardiac surgery. Typically, the platelet count fall begins 5–10 days after starting heparin, although a rapid platelet count fall can occur in a patient who has antibodies from recent heparin use.[54]

Plasmapheresis has been used for treating severe cases of heparin-induced thrombocytopenia.[55]

Cholesterol emboli

Cholesterol emboli are a rare complication of anticoagulant therapy.[56] It occurs 4–8 weeks after anticoagulation therapy. Clinical manifestations depend on the source of the emboli and the corresponding site of their lodgment. Frequent sources are the abdominal aorta, and iliac and femoral arteries. As a result, manifestations are commonly seen in the lower part of the body.[10]

LEARNING ESSENTIALS

- Drugs should always be kept in mind while dealing with cases of purpura and a proper detailed history and examination should be carried out.
- Identification of specific morphological pattern helps in narrowing list of the suspected drug(s).
- A high index of suspicion is especially required for patients on anticoagulants and careful evaluation and systemic association should be sought for.
- Recognition and early withdrawal of offending agent(s) prevents patients from unnecessary investigations and multiple visits.
- Reinstitution of drug is warranted in many cases.

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Chapter

38

Cutaneous Adverse Effects of Corticosteroids Including Topicals

Shyam Verma • Resham Vasani • Grishma Gandhi

SUMMARY

The introduction of topical corticosteroids (TCS) has greatly contributed to the dermatologist's ability to treat various difficult dermatoses. The available range of formulations and potency gives flexibility to treat all groups of patients, different phases of disease, and different anatomic sites. However, increasing use/misuse and over-the-counter availability of these steroid preparations in various fixed combinations have led to increase in cases of steroid-induced side effects. Hence, benefits of rational and ethical use and the harm of overuse and misuse should be clearly conveyed before penning a prescription involving TCS. Similarly, the systemic steroids that are the mainstay of treatment in majority of dermatological disorders that warrant their administration for prolonged periods can also give rise to cutaneous manifestations that serve as a visual reminder to the treating clinician to decrease or stop the offending drug and encourage the early use of steroid-sparing agents.

INTRODUCTION

Steroids are the most potent and most commonly used agents for the treatment of dermatological disorders. They are immensely beneficial in the treatment of various dermatological disorders and do not lead to significant side effects if they are used appropriately in diseases indicated, keeping the potency, duration of therapy, and affected body sites in mind.

The chapter is divided into three sections—cutaneous adverse effects of topical corticosteroids (TCS), cutaneous adverse effects of intralesional steroids, and finally cutaneous adverse effects of systemic steroids. The chapter is written in a question and answer format for easy reading even for non-dermatologists as this information needs to be disseminated to medical professionals at all levels.

CUTANEOUS ADVERSE EFFECTS OF TOPICAL STEROIDS

Why is Topical Steroid Abuse a Significant Problem in India?

TCS are available over the counter (OTC) without a valid prescription and therefore have the maximum potential for being abused by chemists who sell them or even advise buyers about what brands to buy. People also indulge in self-treatment by buying it upon recommendation of family members and friends. Since TCS have been wrongly sold as OTC products, patients buy them as frequently as they wish and even hoard these creams at home for future use. Apart from their abuse in various dermatologic entities, they are also used for achieving fairness of skin, which is an unfortunate reality in this country and even in other parts of the world. Moreover, currently the maximum selling creams are "fixed drug combinations", commonly known as "steroid cocktails", which defy scientific rationale and cause significant side effects (Fig. 38.1). They are abused not only by the unaware patient but also by general practitioners and specialists of fields other than dermatology who are heedless of nuances of topical steroids. Even dermatologists need to share some of the blame for the undeserved popularity of topical steroids as they use them as a "shot gun" treatment for disorders that they are unable to diagnose and/or as a shortcut of sorts.[1] Until very recently, these drugs were outside the Schedule H but at the time of finalizing this article we have received news that steroid creams will now fall under the purview of Schedule H and their sale would be upon prescriptions. Although it is indeed positive news considering the laudable efforts put in by the Indian

Fig. 38.1: Irrational steroid combinations available in the market.

Association of Dermatologists, Venereologists and Leprologists (IADVL), it is yet to be seen whether the implementation will be carried out. Sales figures will be the best indicators of the effect of this welcome new change promised by the government after so many years of chaos.

What are the Solutions for Curbing this Abuse?

The IADVL has formed an Indian Task force Against Topical Steroid Abuse (ITATSA) that seeks to increase the level of public awareness, runs media campaigns, forms study groups for doctors, highlights the problem in lay press and medical journals and holds parleys with state and central authorities. Apart from strong representations that have been made to the Drug Controller General of India to include topical steroids in the list of Schedule H drugs, there is an ongoing follow-up and future activities are planned to continue the fight against topical steroid abuse.[2] As a result of the concerted efforts of ITATSA, the government has finally included these drugs into the Schedule H, a development that needs special mention because IADVL has been eagerly waiting to see the results of their efforts.

How are Steroids Classified according to their Potency?

Human vasoconstrictor assay is the most commonly used method for assessing the potency of TCS.[3] It measures the degree of visible blanching caused by various dilutions of TCS applied to human skin and forms the basis of the current classification system for TCS.

The classification of corticosteroids as per the potency is given in Table 38.1.[4,5]

What are Cutaneous Adverse Effects of TCS?

Box 38.1 enumerates the cutaneous side effects of topical steroids.[6]

Box 38.1: Cutaneous side effects of topical steroids

- Epidermal atrophy
- Hypopigmentation
- Telangiectasia
- Striae
- Epidermal barrier disturbances
- Acneiform eruption
- Steroid addiction or dependence
- Purpura, stellate pseudoscars, and ulcerations
- Infections
- Delayed wound healing
- Alterations in skin elasticity and wound healing
- TCS phobia
- Tachyphylaxis
- Contact sensitization

Epidermal Atrophy

The most common side effect of TCS is atrophy, which affects both the epidermis and the dermis.[6] The chances of atrophy are highest on body areas where the skin is relatively thin, such as eyelids, anogenital area and flexures. The stratum corneum is thin in these areas and also contains numerous

Table 38.1: Potency of TCS

Potency	Class	Topical corticosteroid	Formulation
Ultrahigh	I	Clobetasol propionate	Cream, 0.05%
		Diflorasone diacetate	Ointment, 0.05%
High	II	Amcinonide	Ointment, 0.1%
		Betamethasone dipropionate	Ointment, 0.05%
		Desoximetasone	Cream or ointment, 0.25%
		Fluocinonide	Cream, ointment or gel, 0.05%
		Halcinonide	Cream, 0.1%
	III	Betamethasone dipropionate	Cream, 0.05%
		Betamethasone valerate	Ointment, 0.1%
		Diflorasone diacetate	Cream, 0.05%
		Triamcinolone acetonide	Ointment, 0.1%
Moderate	IV	Desoximetasone	Cream, 0.05%
		Fluocinolone acetonide	Ointment, 0.025%
		Fludroxycortide	Ointment, 0.05%
		Hydrocortisone valerate	Ointment, 0.2%
		Triamcinolone acetonide	Cream, 0.1%
	V	Betamethasone dipropionate	Lotion, 0.02%
		Betamethasone valerate	Cream, 0.1%
		Fluocinolone acetonide	Cream, 0.025%
		Fludroxycortide	Cream, 0.05%
		Hydrocortisone butyrate	Cream, 0.1%
		Hydrocortisone valerate	Cream, 0.2%
		Triamcinolone acetonide	Lotion, 0.1%
Low	VI	Betamethasone valerate	Lotion, 0.05%
		Desonide	Cream, 0.05%
		Fluocinolone acetonide	Solution, 0.01%
	VII	Dexamethasone sodium phosphate	Cream, 0.1%
		Hydrocortisone acetate	Cream, 1%
		Methylprednisolone acetate	Cream, 0.25%

Source: Adapted from Ference and Last.[4]; The WHO Essential Medicines and Health Products Information Portal.[5]

sebaceous follicles, which allows greater penetration of the drug into the dermis. The chances of abuse increase when high-potency steroids are applied and more so under occlusion.

Pathogenesis

Epidermal atrophy is because of suppressive action on cell proliferation, which can occur as early as 3 days following treatment with high-potent TCS. There is suppression of synthesis of stratum corneum lipids, keratohyalin granules, and corneodesmosome.[6]

Dermal atrophy is observed within 3–14 days of treatment because of decreased fibroblast growth and decreased synthesis of collagen 1 and 3 and acid mucopolysaccharides such as hyaluronan synthase 3 enzyme resulting in reduction of hyaluronic acid in extracellular matrix.[7] These changes become irreversible with long-term use of potent TCS.

Clinical Features

Atrophy presents as increased transparency and shininess of skin with appearance of striae, hypopigmentation, and prominent underlying veins (Fig. 38.2).

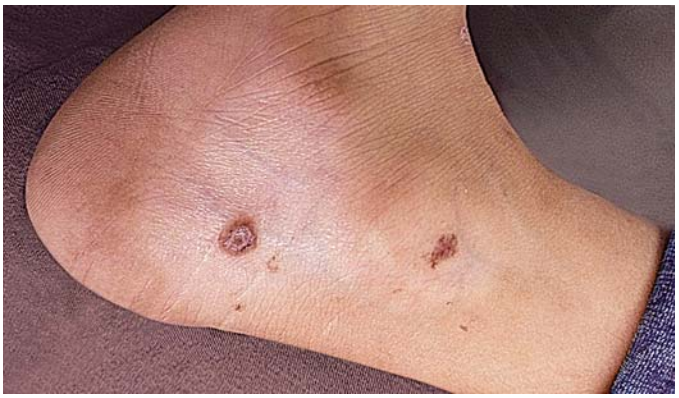

Fig. 38.2: TCS-induced atrophy.

Treatment and Prevention

Topical all-*trans*-retinoic acid prevents TCS-induced skin atrophy without affecting its anti-inflammatory effect.[8]

Steroid-Induced Hypopigmentation

A rather disturbing side effect of TCS application is steroid-induced hypopigmentation that can appear after a few days of inappropriate steroid application (Fig. 38.3). It happens because of inhibition of melanocyte function and responds to withdrawal of the offending topical steroid agent.

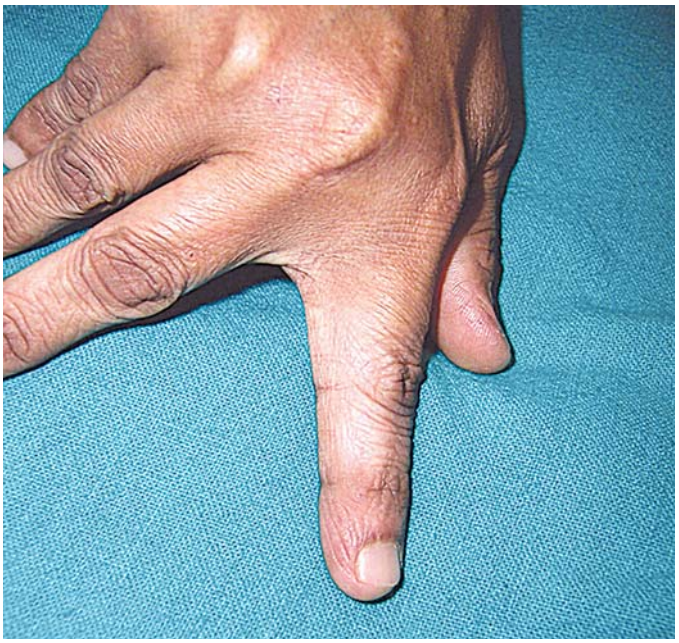

Fig. 38.3: TCS-induced hypopigmentation.

Telangiectasias

Pathogenesis

The use of TCS results in vasoconstriction of the cutaneous vessels because of inhibition of action of nitric oxide (NO). Thus upon withdrawal of application, there will be rebound vasodilatation because of release of endothelial NO. The cycle of repeated vasoconstriction/vasodilation, sometimes called the "neon sign" or "trampoline effect," continues until the vasculature becomes fully dilated as a physiologic response. TCS-induced stimulation of human dermal microvascular endothelial cells has also been implicated in formation of telangiectasias[5,9,10] (Fig. 38.4).

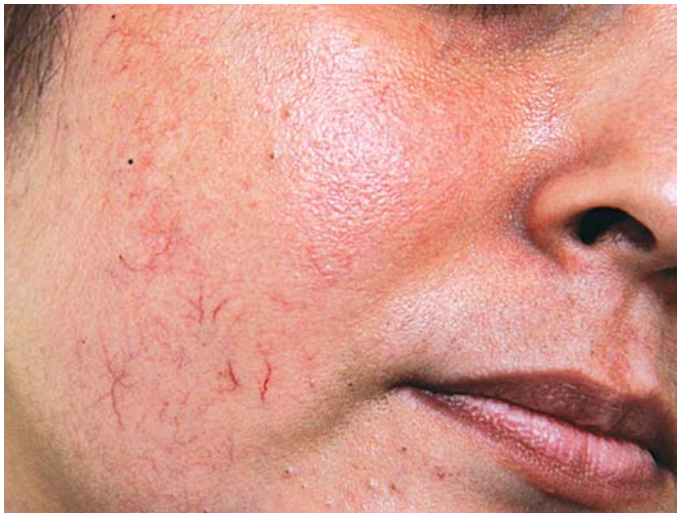

Fig. 38.4: TCS-induced telangiectasias.

Treatment

Most telangiectasias respond to the withdrawal of the TCS and the remaining few can be targeted by sclerotherapy[11] or lasers. The lasers that have been used in telangiectasia whether or not caused by topical steroid abuse include 755 alexandrite,[12] 810 to 980 nm diode[13], potassium titanyl phosphate (KTP)[14] and 1064 neodymium-doped yttrium aluminum garnet (Nd:YAG).[15] Intense pulsed light has also been an effective modality.[16, 17]

Striae (Rubrae Distensae)

Pathogenesis

Initial inflammation and edema of the dermis followed by deposition of dermal collagen along lines of mechanical stress leads to formation of striae. They represent scar tissue and therefore, once developed, are permanent.

Clinical Features

Atrophic striae appear as visible linear scars that form in areas of dermal damage, presumably during mechanical stress.[18,19] (Fig. 38.5). Striae due to corticosteroid abuse should be distinguished from those that occur during excessive weight gain and pregnancy. Striae developing in pregnancy and weight gain are seen on outer aspect of thighs and lumbosacral region in boys; and thighs, buttocks and breasts in girls. Whereas, striae induced by topical steroid therapy occur mostly in flexures and can be unusual in appearance.[20, 21]

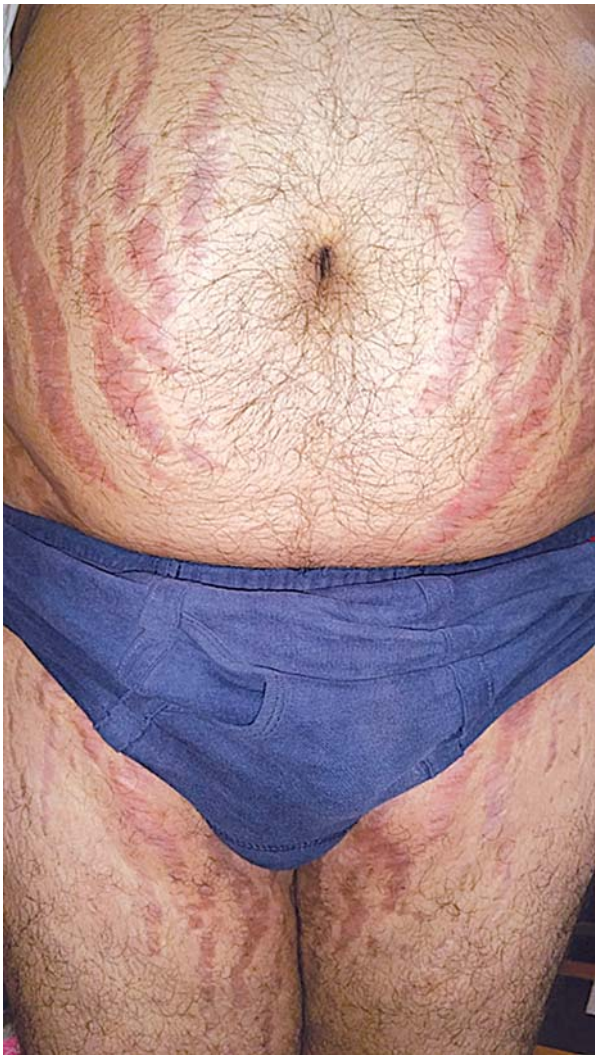

Fig. 38.5: TCS-induced striae.

Treatment

Options tried for striae are topical tretinoin 0.05%,[22] nonablative 1,550 nm fractional Er:glass laser and ablative fractional CO_2 laser resurfacing.[23]

Epidermal Barrier Disturbance

Decreased formation of lipid lamellar bodies and delayed barrier recovery (i.e. increased transepidermal water loss) due to the effect of high-potency TCS application lead to subtle impairment of barrier function of the skin.[24, 25]

Steroid-Induced Acneiform Eruption

Etiopathogenesis

Topical steroids render the follicular epithelium more responsive to comedogenesis. They lead to increased concentration of free fatty acids in skin surface lipids and proliferation of *Propionibacterium acnes* in the pilosebaceous duct which in turn contribute to aggravation of preexisting acne and can lead to an acneiform eruption.[26, 27]

Clinical Features

Acneiform eruption consists of small and uniformly sized (monomorphic) inflammatory papules and pustules with few or no comedones developing over the area of application (Fig. 38.6). Factors predisposing are higher concentration of the drug, application under occlusion, younger adults, whites in preference to blacks, and application on acne prone areas of face and upper back.

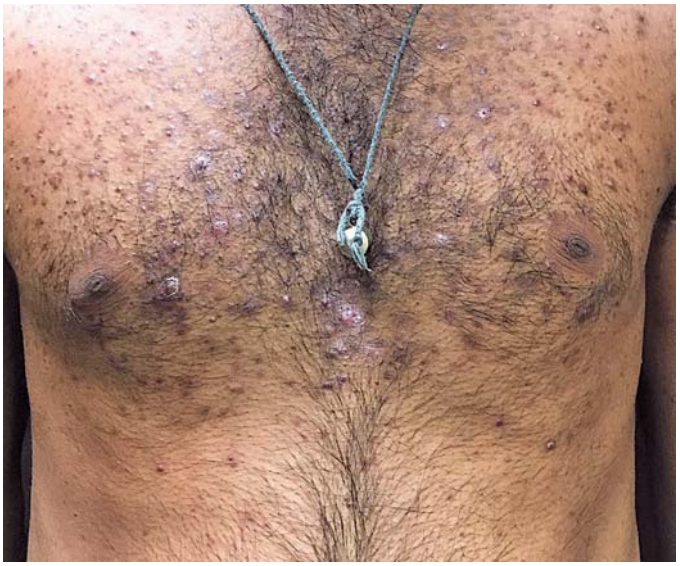

Fig. 38.6: TCS-induced acneiform eruption.

Treatment

Cessation of the culprit corticosteroid is the mainstay. Topical tretinoin 0.025% once at night for 2–3 months is effective. Oral antibiotics with anti-inflammatory activity such as tetracyclines and macrolides are also effective. Other anti-acne agents such as topical benzoyl peroxide has both anti-inflammatory and antimicrobial effects and is hence very effective.[28, 29, 30]

Topical Steroid Addiction and Dependence

Topical steroid addiction is a result of chronic abuse of TCS and results in physiological and psychological dependence on the drug. When the patient attempts to stop the topical steroid, there is a flare-up of symptoms, leading to physical and psychological distress to the patient. Therefore, the patient feels the need to continue using TCS. Any attempt to stop treatment leads to severe rebound inflammatory edema, redness, burning sensation and a possible acute pustular eruption 4–10 days after stopping TCS application and usually lasts for a few days to 3 weeks.

Many patients give in to the temptation of restarting the application to suppress this undesirable effect and thus become dependent on the application of corticosteroids.[31]

Etiopathogenesis

The potential for causing addiction is directly related to the potency and duration of application of TCS. It requires about 2–4 months of use to produce this condition.

Topical steroid dependence manifests itself as the following conditions.

Topical Steroid Damaged Face

Symptom complex of the various side effects caused due to unsupervised application of steroids on face is now described as topical steroid damaged face (TSDF).[32] There are two scenarios in which this situation is commonly encountered. The first, where TCS are prescribed for the correct indication but the patient continues to apply them unsupervised for prolonged periods. And the second, when the patient applies the steroid or steroid-containing combination cream for the wrong indication such as acne or worse, to lighten the facial skin. Any attempt to stop treatment leads to a distressing rebound. The symptom complex consists of erythema, papules, pustules, rosacea-like appearance, comedones, hypopigmentation, hyperpigmentation, telangiectasia, hypertrichosis, perioral dermatitis, or allergic contact dermatitis with or without associated photosensitivity (Fig. 38.7). Corticosteroid withdrawal is characterized by erythema and flare for 2 weeks followed by desquamation.[33]

Steroid-induced Rosacea-like Dermatitis

This is also known as "iatrosacea" and "topical steroid-induced rosacea-like dermatosis". The condition is characterized by a flaming red, scaly, papule-covered face (red face syndrome) or at times has a perioral or centrofacial distribution. Symptoms include severe discomfort, pain, sensations of tightness, moderate burning or stinging, dryness, and occasionally intense pruritus. It takes between 2 and 6 months of TCS application to produce such a clinical picture. Such symptomatology can also be a part of TSDF.[34]

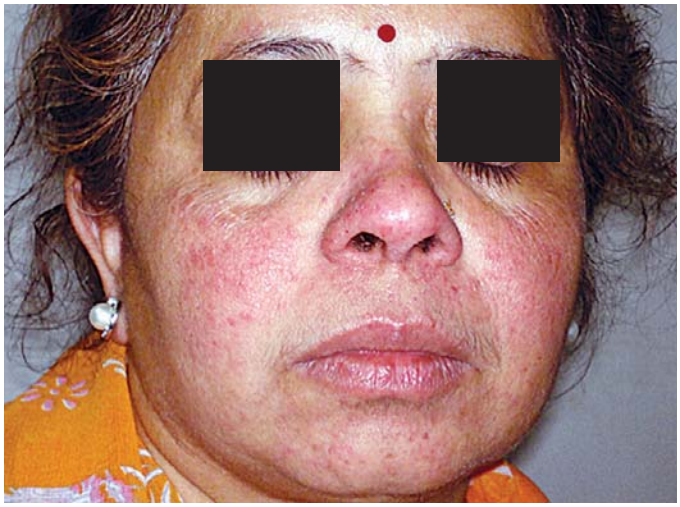

Fig. 38.7: Topical steroid damaged face.

Etiopathogenesis

It is believed to be due to local immunosuppression caused by TCS application leading to increased proliferation of *Demodex folliculorum* and *P. acnes* causing a rosacea-like condition.

Clinical Features

Steroid dermatitis has been classified according to localization into three types: Perioral, centrofacial, and diffuse type.

Perioral type: Presents discrete-to-moderate erythematous papules and pustules located around the mouth with a clear zone 3–5 mm below the lower lip (Fig. 38.8). Steroid-induced perioral dermatitis is differentiated from common perioral dermatitis by history and clinical examination. The former has more erythema, inflammation, and scaling.[35,36]

Centrofacial type: Cheeks, lower eyelids, nose, forehead, and glabella are affected with sparing of perioral region.

Diffuse type: The entire face, forehead, and neck are affected (Fig. 38.9).

Children often present with perinasal and periocular lesions, as well as lesions in the classical perioral site.[37]

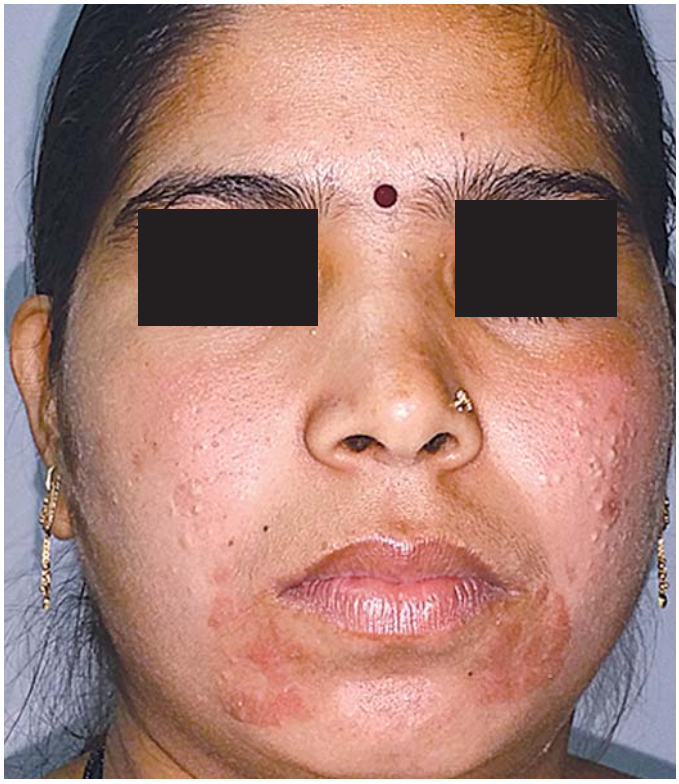

Fig. 38.8: Perioral dermatitis.

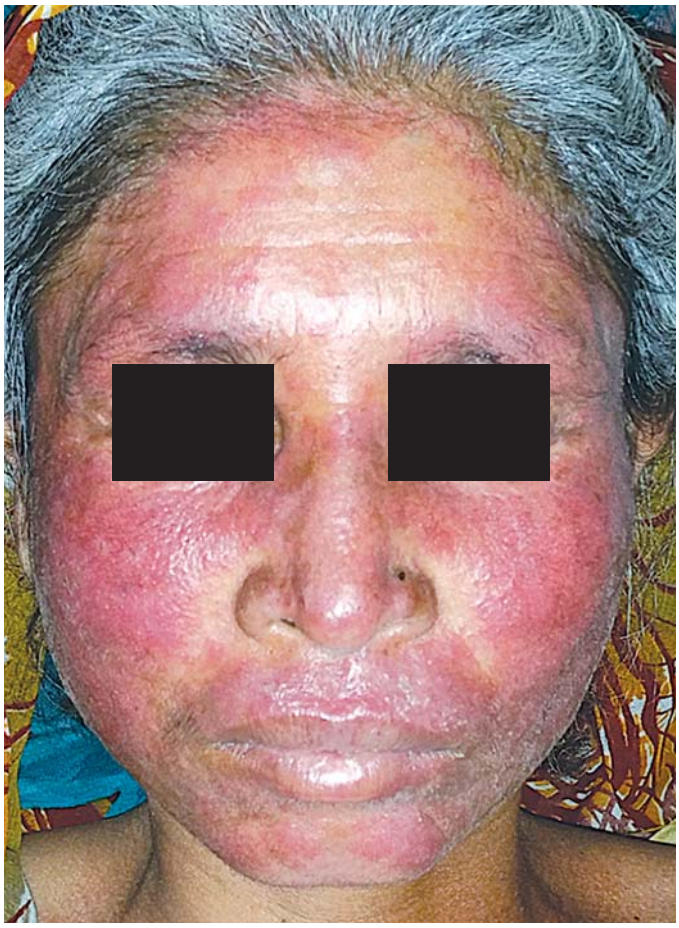

Fig. 38.9: Diffuse variant of topical steroid-induced rosaceiform eruption.

TCS Abuse of the Genital and Perianal Area

Presents as a condition known as "red scrotum syndrome" (RSS), which manifests as burning and erythema of the anogenital region, scrotal pain, and in later stages atrophy of the glans.

RSS can develop after prolonged use of TCS like in the red face syndrome.

The major symptoms are neurological. Although it mimics eczema on a first glance, morphology and course are quite different. Burning and hyperalgesia are the predominant symptoms as against itch in eczema/dermatitis. This argues for a possible neurogenic inflammation. Indeed, RSS resembles erythromelalgia.

TCS abuse of female genitalia presents as persistent pruritus vulvae and vulvodynia, which worsens upon withdrawal of TCS.[31] Topical steroid abuse of perianal area presents as persistent perianal erythema and burning, which occurs as a manifestation of rebound phenomenon.

Management of Topical Steroid Dependence

Educating and counselling the patient is of utmost importance. One can exercise the choice between stopping TCS abruptly or perhaps more conveniently, gradually weaning the patient off the steroid by using a lower potency molecule and reduce its frequency as rapidly as possible. Fluorinated steroids such as betamethasone valerate, betamethasone dipropionate, triamcinolone acetonide, and dexamethasone have a propensity to cause rosacea-like dermatitis as well as atrophy and telangiectasia. They should be replaced by nonfluorinated steroid molecules. After the acute phase is over, the patient can be maintained on topical calcineurin inhibitors such as pimecrolimus or tacrolimus, though some patients experience a burning sensation especially after application of tacrolimus. They need to be advised to avoid sunlight, use sunscreens and use mild cleansers containing cetyl/stearyl alcohol after washing with plain or lukewarm water. Doxycycline, minocycline, or metronidazole can be used orally when the rosacea component dominates the clinical picture. Bland emollients for dryness, antihistamines for itching, cold water compresses for burning sensation, burrow's solution for oozing lesions, oral antifungals for pityrosporum folliculitis and ivermectin for demodicosis may be used as and when the situation demands. Oral anxiolytics may be added in severe cases.[32, 38] Recently, role of tranexamic acid has been evaluated for treatment of rosacea. Tranexamic acid both orally and topically improves epidermal barrier

function by inhibiting serine proteases.[39] Brimonidine tartrate (0.33%) gel has also been recently shown to be useful in rosacea on a temporary basis on account of its α2-adrenergic agonist action. It causes direct vasoconstriction of both the small arteries and the veins.[40]

Management of Red Scrotum

Various agents have been reported to be useful in the treatment. Doxycycline for 2 weeks has been tried as first-line agent failing which gabapentin and pregabalin have been given as second-line treatment. The effective use of pregabalin and gabapentin also endorse a neuropathic etiology in causation of the syndrome.[41-44]

Purpura, Stellate Pseudoscars and Ulcerations

As mentioned earlier, abuse of TCS causes dermal atrophy and loss of intercellular substance. This causes blood vessels to lose their surrounding dermal matrix. This renders dermal vessels fragile and produces purpuric, irregularly shaped, hypopigmented, depressed and at times, stellate scars. Severely atrophic, telangiectatic skin over the extremities is prone to developing these scars.[45]

Hypertrichosis

Steroids promote vellus hair growth by an unknown mechanism. Local and disseminated hypertrichosis due to TCS is not as commonly seen as with systemic steroids (Fig. 38.10).[36]

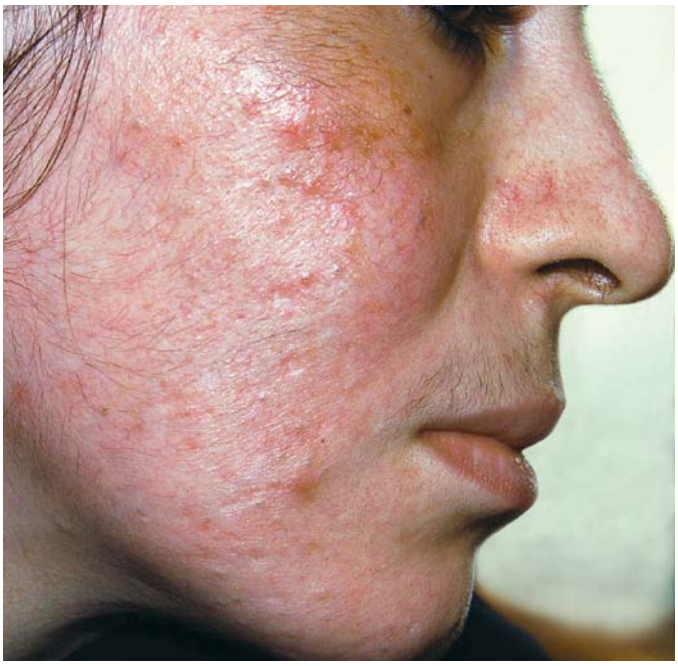

Fig. 38.10: TCS-induced hypertrichosis.

Infections

Mucocutaneous infections such as dermatophytosis, pityriasis versicolor and onychomycosis due to *Trichophyton* and *Candida* species tend to get aggravated or even modified by the application of TCS resulting in misdiagnosis and wrong management by nondermatologists and quacks.

Dermatophytosis

The rampant misuse of TCS majorly accounts for the growing number of atypical presentations of dermatophytosis including bizarre morphology and involvement of large body areas. An increasing number of cases of male genital involvement have been recently reported.[46] Also being reported is widespread "nonresponse," "partial response," and "recurrence" of the disease following conventional doses of antifungals. The various morphological variations of steroid-modified tinea/tinea incognito that are being reported include eczematous lesions, tinea with double edges also known as tinea pseudoimbricata (Fig. 38.11), multiple coalescing annular lesions, ill-defined lesions on face with barely perceptible borders, pustular lesions, etc. Steroid-modified tinea often shows accompanying side effects of TCS such as hypopigmentation, striae, telangiectasias and even contact dermatitis.[46]

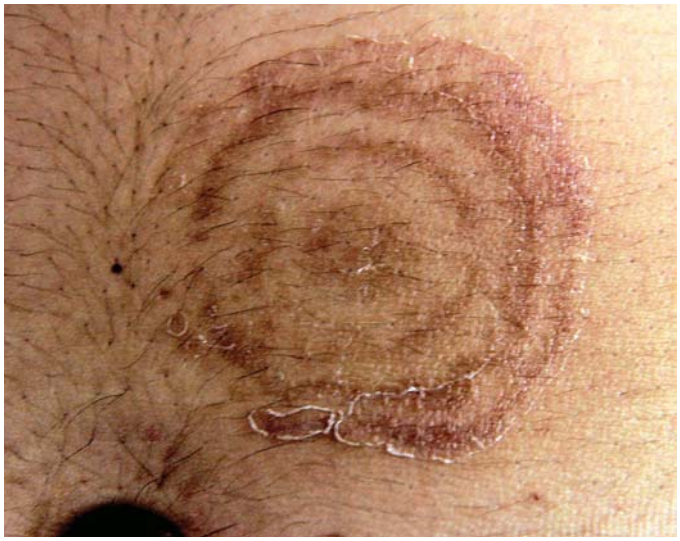

Fig. 38.11: Tinea pseudoimbricata due to TCS misuse.

Granuloma Gluteale Infantum

This is a persistent reddish purple, granulomatous, papulonodular eruption on the buttocks and thighs of infants. It occurs when diaper dermatitis is treated with topical steroids (Fig. 38.12).

Similar effects on mitigation or prolongation of herpes simplex, molluscum contagiosum, and scabies

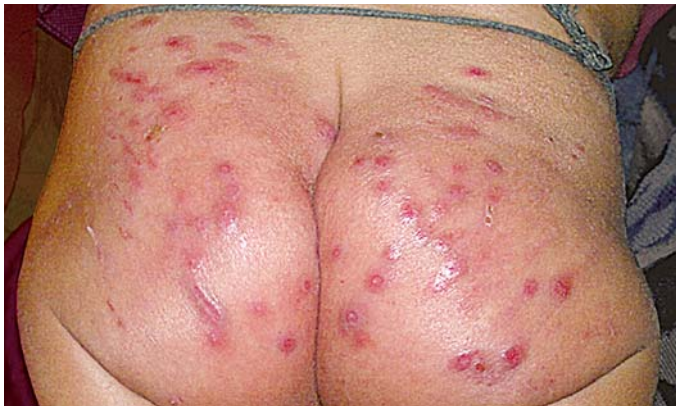

Fig. 38.12: Granuloma gluteale infantum.

infection have also been reported; hence TCS should not be used in presence of these infections.[36]

Delayed Wound Healing

TCS are known to have a significant effect on wound healing. Glucocorticoids are known to reduce the levels of procollagen mRNA and mRNA synthesis in unwounded cells thereby reducing type 1 procollagen synthesis.[47] This, in turn, results in incomplete granulation tissue formation and reduced wound contraction. Corticosteroids also reduce the levels of transforming growth factor beta (TGF-β) and insulin-like growth factor 1 (IGF 1) in wounds thus affecting normal wound healing. It has also been shown that retinoids to some extent reverse this effect and hence could be helpful in reducing the incidence of this side effect.[47-50]

Alterations in Skin Elasticity and Mechanical Properties

Decrease in skin elasticity is a common complication of TCS therapy. It can be assessed easily by pulling skin and observing incomplete retraction upon cessation of mechanical stress. In addition, skin extensibility can also be demonstrated, which refers to the ability of skin to be elongated due to rarefaction of dermal connective tissue.[36]

Skin Ageing and Influence of Sun

Significant decrease in skin thickness, especially in light-exposed areas and delayed skin recovery are reported.[36]

TCS Phobia

TCS phobia is a phenomenon that is born out of ill understood or ill perceived awareness regarding topical steroid abuse from various sources including electronic media. It affects compliance adversely. It is commonly encountered in patients of atopic dermatitis and is more common in females. Judicious counselling regarding use and abuse of steroids is imperative in preventing such a reaction.[38]

Tachyphylaxis

The possible downregulation of the glucocorticoid cell receptor results in desensitization to the effect of glucocorticoids. This phenomenon is called tachyphylaxis and probably should be rechristened as "bradyphylaxis," since it is supposed to denote "a slow, progressive decreasing response to treatment over long periods of use."[51] The patient usually complains that the once effective TCS no longer work as well as it used to in the past.

Contact Sensitization

Halogenation stabilizes the corticosteroid molecule and renders it less prone to degradation with a less potential for sensitization. Nonfluorinated corticosteroids have been found to be more likely associated with contact allergy in comparison.[52, 53]

Corticosteroids (CS) have been classified according to their cross-reacting properties into four classes as in Table 38.2.[54]

WHAT ARE THE SPECIAL PRECAUTIONS TO BE TAKEN WHILE PRESCRIBING TCS IN CHILDREN?

Special Considerations regarding use of TCS in Children

Children, especially infants, are more susceptible to adverse effects of TCS due to their inadequate ability to metabolize potent corticosteroids. Also, the increased skin surface area: body weight ratio leads to increase in systemic absorption. This can lead to suppression of hypothalamic pituitary adrenal axis. Cushing syndrome and slowing of linear growth of infants and children because of suppression of endogenous cortisol production are also reported.[55,56] Following precautions should be taken while prescribing TCS to infants and children.[57]

- Potency: Preferably prescribe a low-potency TCS, for short durations.[58]

  Potent steroids should be avoided except in conditions with thickened skin such as lichen planus, psoriasis, lichen simplex chronicus, etc.
- Site: Avoid application under occlusion in the nappy area or any other occluded area. The diaper region is vulnerable to increased local side effects as well as systemic absorption because of increased moisture, maceration, friction, and occlusion by diaper. Same logic applies to the use of topical steroids on face, eyelids, and

Table 38.2: Classification of topical corticosteroids as per the cross reactivity

Structural class	Class A: Hydrocortisone type	Class B: Triamcinolone acetonide type	Class C: Betamethasone type	Class D1: Betamethasone dipropionate type	Class D2: Methylprednisolone aceponate type
Structure	No substitutions in the D ring, except C21 short-chain esters	C16,17- cis -diol or -ketal	C16-methyl substitution	C16-methyl substitution C17/C21-long-chain ester	C16-no methyl substitution C16-no halogenation C17-long-chain ester C21-possible side chain
Cross-reactions	Cross-reacts with D2	Budesonide specifically cross-reacts with D2			Cross-reacts with class A and budesonide
Patch test substance	Tixocortol-21-pivalate	Budesonide Triamcinolone acetonide		Clobetasol-17-propionate	Hydrocortisone-17-butyrate

axillae. Hence, lowest potency steroids for a valid indication for the shortest duration possible are to be advised in such circumstances.

- Frequency of application: Lowest potency TCS should be used once a day if possible. Consider alternate days or even weekend and weekday therapy, which have been shown to have comparable efficacy and superior side effect profile.
- Steroid-sparing agents: Steroid-sparing agents such as topical calcineurin inhibitors, topical antipruritic agents, emollients to alleviate xerosis in atopic dermatitis, and topical antimicrobials to combat infection are to be supplemented as early as possible.
- Supportive measures: Supportive measures such as reduction of weight in obese patients, control of sweat by absorbent dusting powders, keeping the skin dry, avoiding wet clothing can help in reducing the need and hence the side effects of TCS.

  Table 38.3 elaborates the amount of steroid in terms of fingertip unit (FTU) that can be safely applied on children.[59]

Table 38.3: Guidelines for steroid application in children

Anatomic areas	**FTU required**	**Amount needed for twice daily regimen in gram**		
	3–6 months	1–2 years	3–5 years	6–10 years
Face and neck	1/1	1.5/1.5	1.5/1.5	2/2
Arm and hand	1/1	1.5/1.5	2/2	2.5/2.5
Legs and foot	1.5/1.5	2/2	3/3	4.5/4.5
Anterior trunk	1/1	2/2	3/3	3.5/3.5
Posterior trunk and buttocks	1.5/1.5	3/3	3.5/3.5	5/5

Source: Adapted from Long CC, Mills CM, Finlay AY. Br J Dermatol 1998; 138: 293–296.

HOW TO OPTIMIZE THE USE OF STEROIDS IN CLINICAL PRACTICE?

- **Counsel the patient**

  Counselling is vital regarding the amount, frequency of application, duration of use, and potency of various steroid preparations, whether to apply with or without occlusion.

- **Amount of application**

  Rule of hand: This rule states that area of the size that can be covered by four adult hands (including the digits) can be treated by 1 g or two FTUs.[60]

  FTU is the amount of ointment squeezed from a tube to cover an area from the distal interphalangeal crease to the distal tip of the finger (Fig. 38.13). When squeezed from a standard 5 mm diameter nozzle, this amount of ointment weighs about 0.5 g for a male and 0.4 g for female. For infants and children, one-third the amount used for adults is used. It takes about 20–30 g cream to cover the entire body of an adult in a single application (Fig. 38.14). It is prudent not to use more than 45 g/week of superpotent or 100 g/week of a potent steroid. The relation between FTU and rule of hand is as follows: 4 hand areas = 2 FTU = 1 g.[61,62]

- **Frequency of application**

  TCS are known to have a "reservoir effect" and it is the stratum corneum that is the reservoir here. This effect is more in high-potency steroids. Most steroids are recommended to be applied once or twice a day. Alternate days or weekend therapy may be useful for chronic conditions requiring maintenance therapy.[63]

- **Duration of application**

  The optimum duration of treatment for acute

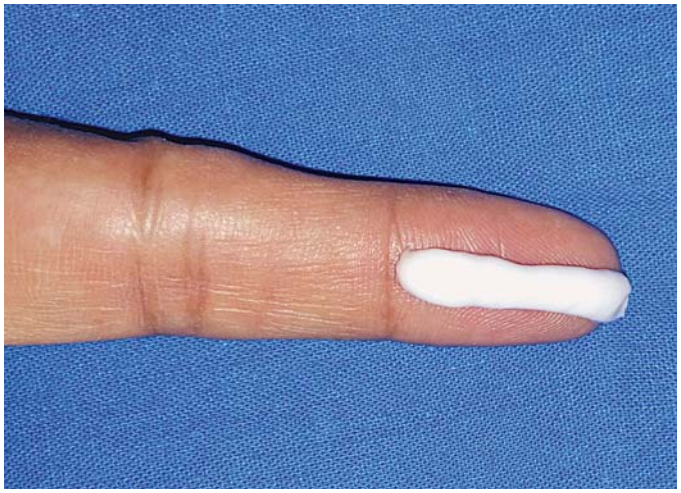

Fig. 38.13: Uniform amount of ointment squeezed from a tube having a nozzle 5 mm in diameter, extending from the distal interphalangeal crease to the distal tip of the finger represents the finger tip unit (FTU) & weighs about 0.5 g for an adult male.

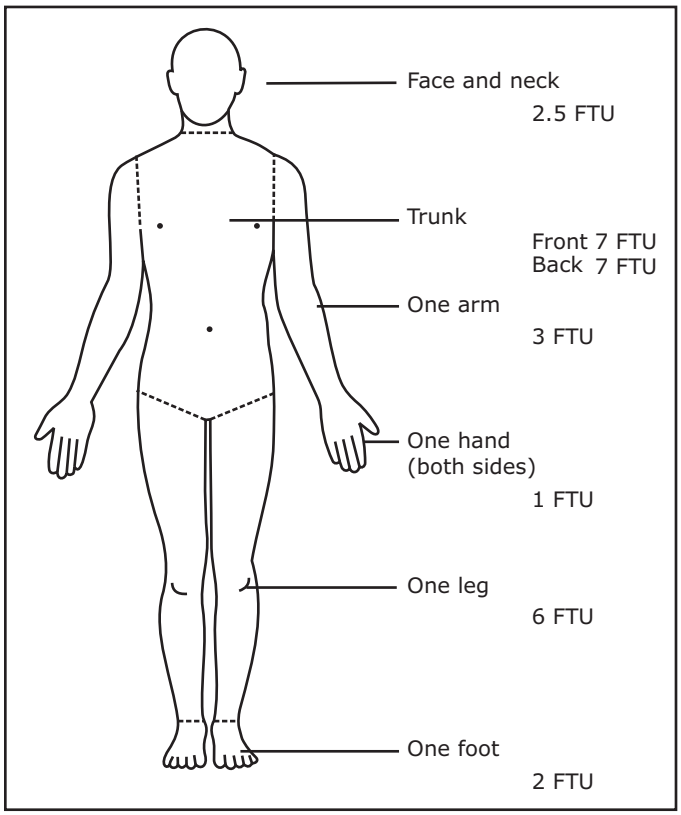

Fig. 38.14: An approximate estimation of the number of finger tip units (FTUs) of cream required to cover the entire body of an adult in a single application considering 1 FTU to be 0.5 gram. (Figure adapted from Long CC, Finlay AY, Averill RW. The rule of hand: 4 hand areas=2 FTU=1 g. Arch Dermatol 1992; 128 (8): 1129–30.60).

skin conditions on face should be no more than 2 weeks and 3–4 weeks for the rest of the body. Studies indicate that ultrapotent steroids should not be used for more than duration of 3 weeks.[64]

Differences in Choice of Topical Steroid as per the Location of Application

Absorption of TCS varies from site to site. There is minimum penetration of TCS in areas with a thick stratum corneum such as palms and soles and therefore, the use of high-potency TCS preparations is warranted. Areas such as the scrotum, eyelids, or occluded areas such as intertriginous region allow rapid and extensive drug penetration leading to increased systemic absorption. It is prudent to use a low-to-mid-potency TCS in dermatoses involving large areas of skin. Avoid application on macerated, moist, intertriginous skin.

Measures Adopted to Improve the Penetration of TCS

- **Prehydration**: Hydrating the skin by bathing or sponging before applying the TCS improves penetration and hence efficacy.
- **Occlusion**[65,66]: Occlusion by application of dressings such as wet wraps, plastic wraps, or hydrocolloid dressings increases the penetration of TCS. The permeability of the drug increases almost 10-fold under occlusion.
- **Choice of vehicle**[64]: The choice of preparation depends on the type of lesion and anatomic region affected. Ointments consist of oleaginous bases such as petrolatum, which provide hydration to the stratum corneum by acting as an occlusive barrier. Ointments are ideal for the management of dry, scaly or lichenified lesions and on areas with thick skin (palms and soles). They are associated with occlusion folliculitis, maceration and poor patient compliance due to their greasiness. Creams provide lubrication, easily vanish into skin when applied and are more spreadable and easily washable. Creams are preferred over ointments in case of oozing and exudative lesions and for intertriginous sites. Lotions and gels, on other hand, are least occlusive and penetrative and have better spreadability hence preferred for scalp. Lotions are preferred in children because of their more permeable skin.

CUTANEOUS SIDE EFFECTS OF INTRALESIONAL CORTICOSTEROIDS

Atrophy and hypopigmentation are the most common side effects. The cause of hypopigmentation is not clear. Linear extension of hypopigmentation is thought to be due to lymphatic uptake of steroid crystals (Fig. 38.15). Triamcinolone is more likely to cause depigmentation due to its larger size, the higher tendency to aggregate, and higher density. It has been

proposed that steroids may reduce the number or activity of melanocytes,[7] presumably by unintentional migration of the steroid in the proximity of the injection site or by improper injection technique. Steroid ulcers can be a presentation on long-term use of intralesional steroids at the same site.

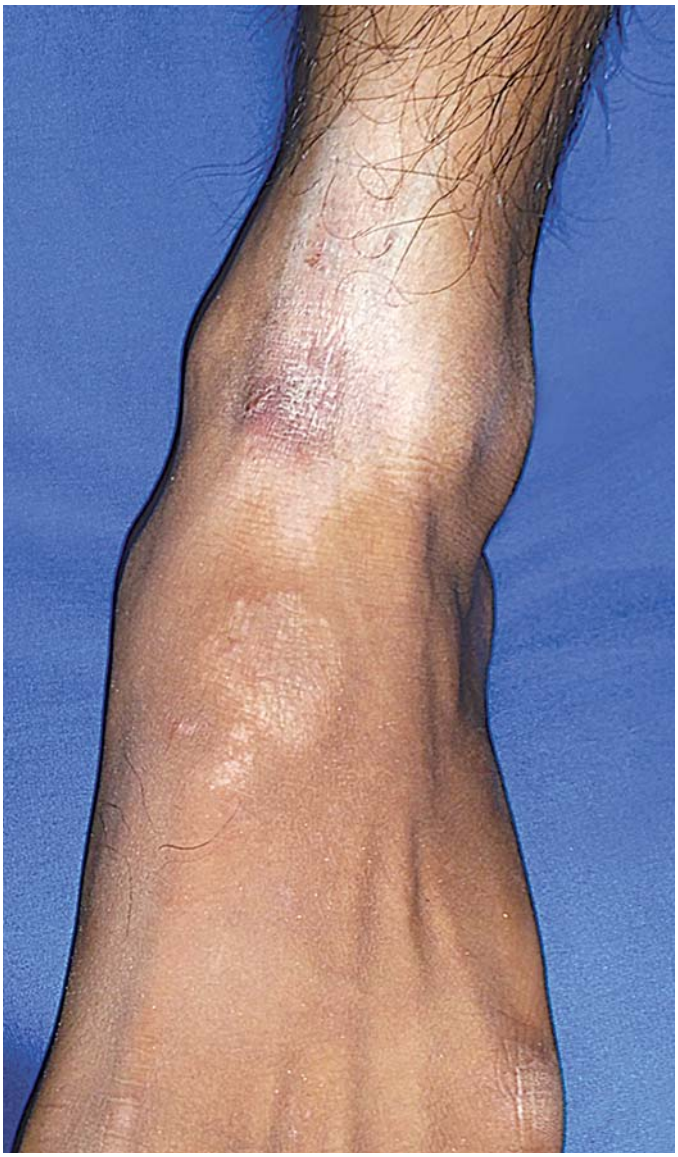

Fig. 38.15: Linear depigmentation due to intralesional steroid use.

CUTANEOUS SIDE EFFECTS OF SYSTEMIC CORTICOSTEROIDS

Systemic steroids can be administered through oral, intramuscular or intravenous route. Various CADRs have been observed which can be categorized as follows:

i. Wound healing and related changes

Administration of high corticosteroid levels in the early stages of wound healing has been shown to delay the appearance of inflammatory cells, fibroblasts, the deposition of collagen, the regeneration of capillaries, contraction, and epithelial migration. These wounds essentially fail to exhibit an inflammatory response.[67,68] They manifest as nonhealing wounds, ulcers, striae, atrophy & telangiectasias.

ii. Pilosebaceous related

Corticosteroids lead to proliferation of *Pityrosporum ovale*, androgenicity, ↑ seborrhea, follicular hyperkeratosis with occlusion & inflammation. "Steroid acne", "steroid rosacea" and even acne following inhaled corticosteroid has been reported.[69]

iii. Vascular related

Catabolic effects on vascular smooth muscle, ↑ skin fragility & loss of subcutaneous tissue are reported with CS resulting in purpura (Fig. 38.16), including actinic purpura & "blot hemorrhages".[70]

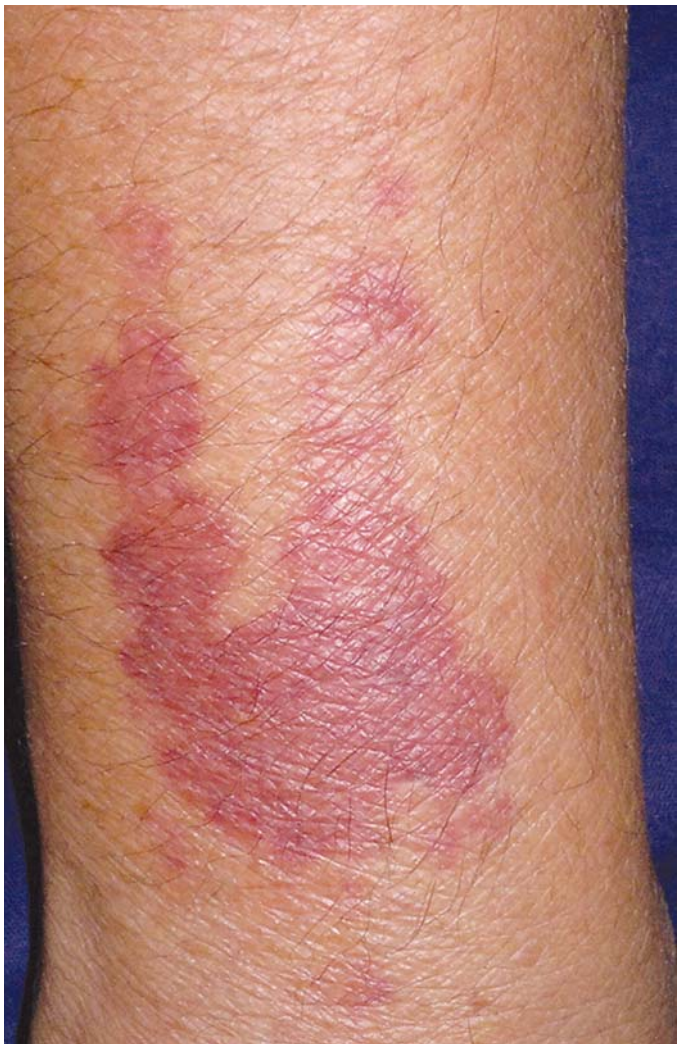

Fig. 38.16: Loss of subcutaneous fat and purpura due to systemic steroid use.

iv. Cutaneous infections

Corticosteroids inhibit the immune system and increase susceptibility to infections including those associated with live vaccines. Infection can spread rapidly, may have an atypical presentation and the severity may be masked.[71,72] Varicella may cause fatal illness in children taking long-term CS therapy. It is necessary to vaccinate the child prior to starting the treatment.[72]

v. Hair effects

CS leads to growth of vellus hair by uncertain mechanism with resultant hypertrichosis as a CADR (Fig. 38.17).[70]

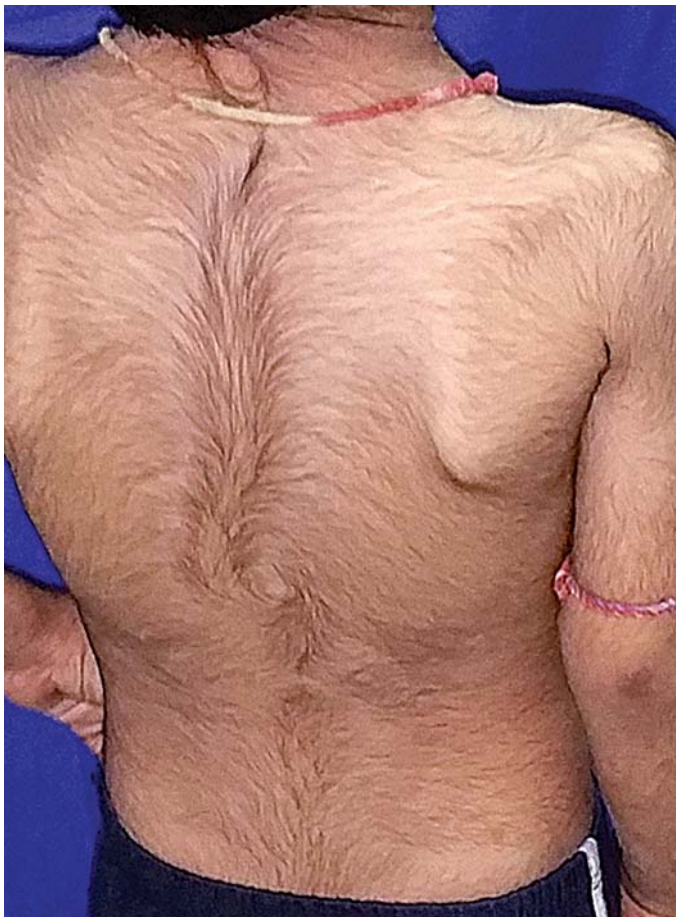

Fig. 38.17: Generalized increase in vellus hairs in a child of nephrotic syndrome on systemic steroids.

vi. Allergic cutaneous reactions

Allergic reactions following systemic administration of CSs have rarely been reported in the literature, most commonly being immediate in nature. Depending on various routes of administration of CS they are as follows[73]:

a. Oral: Maculopapular rash, urticarial rash and angioedema, flare-up of dermatitis, facial edema, erythema multiforme–like eruption.
b. Intramuscular: Generalized rash, urticaria, and anaphylaxis
c. Intravenous: Pruritic rash, purpura, anaphylaxis
d. Inhalational: Urticarial, erythema, pruritus, facial rash

vii. Adipose tissue and dermis related changes

Prolonged corticosteroid therapy commonly causes weight gain and redistribution of adipose tissue that result in cushingoid features - truncal obesity, facial adipose tissue i.e. moon face (Fig. 38.18) and dorsocervical adipose tissue. Risk factors for their development are use of CS for 2–3 months, excessive caloric intake, young patient & higher baseline BMI.[74,75]

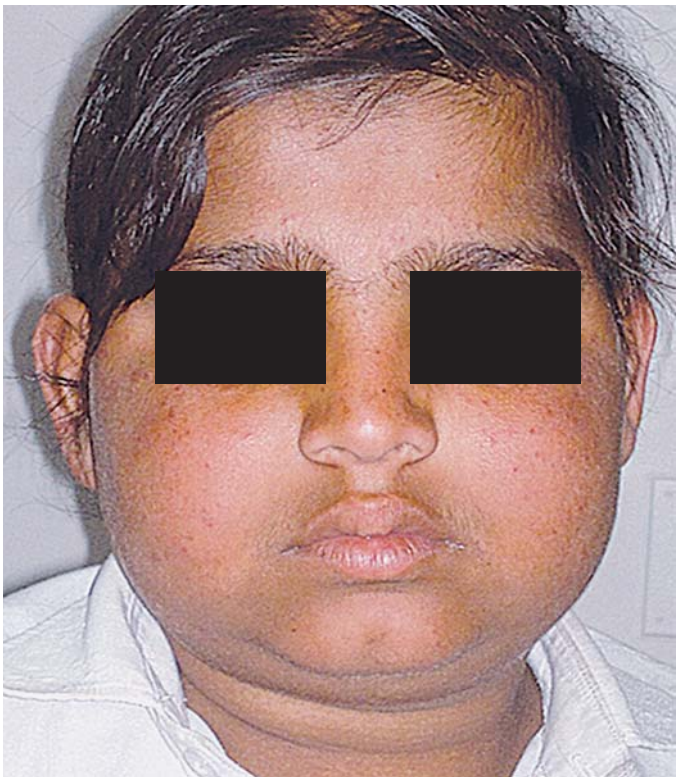

Fig. 38.18: Cushingoid facies.

Stretching of the fragile skin due to the enlarging trunk, breasts, and abdomen leads to development of broad, reddish-purple striae. The red-purple livid striae greater than 1 cm in width which is typical, and almost pathognomonic, are most commonly found over the abdomen (Fig. 38.19), but are also present on the upper thighs, breasts, and arms.[76]

Generalized cutaneous atrophy is another effect common with systemic treatment. Risk factors appear to be female sex, prolonged treatment, and high dose.[77]

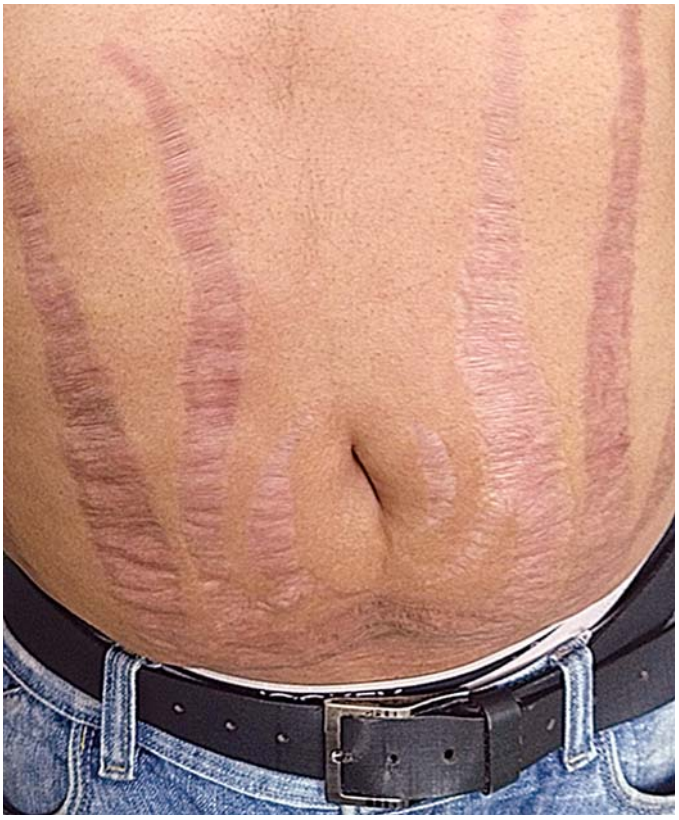

Fig. 38.19: Livid reddish- purple striae over abdomen as part of Cushingoid features due to systemic steroids.

Injectable CS related

They cause lipolysis of subcutaneous fat leading to fat atrophy (Fig. 38.20), crystallization of injectable material and predisposition to cutaneous tuberculosis, and atypical mycobacterial abscess.[78]

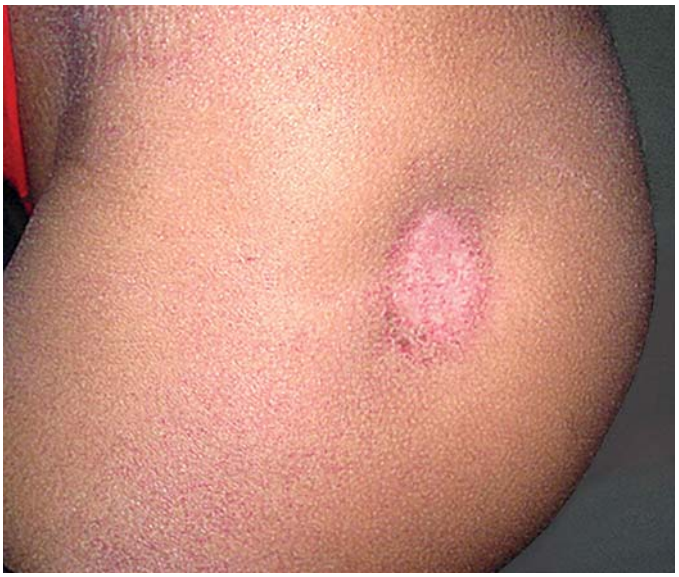

Fig. 38.20: Depigmentation and lipoatrophy due to intramuscular injection of triamcinolone acetonide injection.

Miscellaneous

Tapering of systemic CS may precipitate flare up of pustular psoriasis & rebound of poison ivy/ oak dermatitis. Insulin resistance caused due to CS can manifest as acanthosis nigricans (Figs. 38.21 A and B).

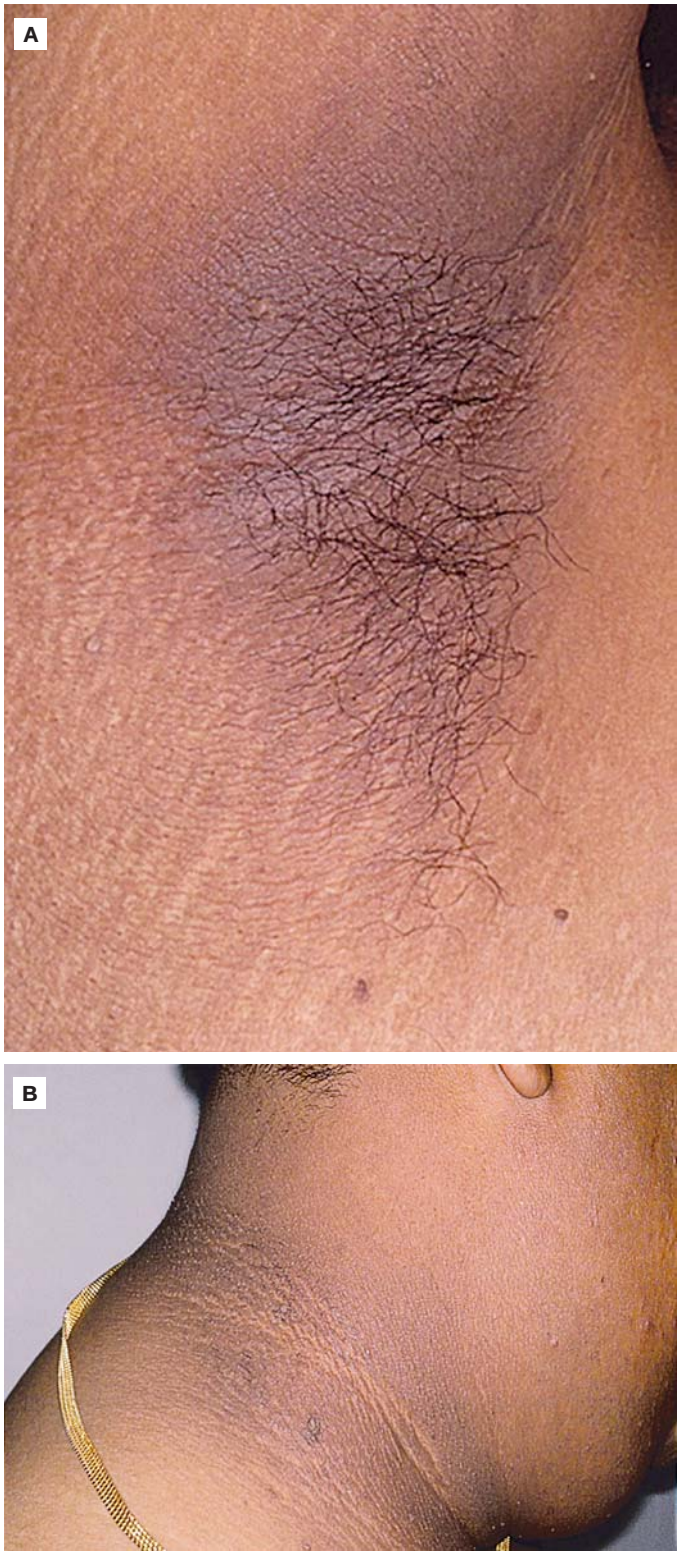

Fig. 38.21: (A & B) Acanthosis nigricans.

CONCLUSIONS

With the appropriate and judicious use of CS, it has become so much easier to treat a variety of dermatoses in an effective manner thus bringing quick relief to patients. However, improper use particularly of topical corticosteroids (TC) in approved and non-approved indications has resulted in some well-defined adverse effects including steroid specific dermatoses. Awareness of CS related adverse effects will help to put in place urgent preventive and therapeutic measures. Temptation to use CS for undiagnosed rash or using TC in combination therapies which are expensive and of unproven additional advantage should be resisted. Rational and ethical use of TC should continue to be promoted through multipronged approach involving medical fraternity, pharmaceutical industry, and political and legal establishment.[79]

LEARNING ESSENTIALS

- Correct diagnosis of the clinical condition and choosing an appropriate topical corticosteroid according to the affected area, patient's age, clinical presentation and predicted responsiveness to treatment is most important.
- Children are more prone to the systemic adverse effects of TCS because of poorly developed barrier function and a large surface area to weight ratio compared to adults.
- Strategies for early and efficient withdrawal of TCS and substitution by steroid sparers and emollients can help in preventing development of TCS related side effects.
- Increased awareness about topical corticosteroid abuse in patients and the nondermatologists is vital and so are initiatives toward curbing the OTC sale of TCS. An IADVL initiative ITATSA is contributing to this cause in a big way.

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Chapter

39 Cutaneous Adverse Drug Reactions to Miscellaneous Immunomodulator Drugs

Krina Bharat Patel

SUMMARY

Miscellaneous immunomodulator drugs are frequently used for inflammatory and immune-associated cutaneous disorders. As these drugs are often used for a prolonged period, drug reactions are not uncommonly encountered. While mild cutaneous adverse drug reactions (CADRs) are more frequent, some of the drugs are associated with severe cutaneous reactions with prolonged course and life threatening consequences due to systemic associations. Dapsone hypersensitivity syndrome (DHS), antimalarial-induced lupus erythematosus are few of the serious CADRs observed.

INTRODUCTION

A variety of immunomodulator drugs have been used in various dermatological disorders, on account of their observed beneficial effects. Apart from known immunosuppressives like steroids and antimetabolites, there are many miscellaneous drugs which act as immunomodulators in a particular disease. As most of these drugs are used for extended period of time, i.e. at least for more than 4 weeks, they may lead from mild to severe kind of cutaneous drug reactions. A brief summary of the cutaneous adverse drug reactions (CADRs) reported due to common immunomodulatory drugs has been described later.

DAPSONE

Dapsone (4,4'-diaminodiphenylsulfone, DDS) is a well-known antileprosy drug but has also found its place in treatment of many inflammatory cutaneous disorders owing to its effect in altering neutrophilic function and also its effect on eosinophils and monocytes. Food and Drug Administration (FDA) has approved use of dapsone in dermatitis herpetiformis and leprosy. Other common dermatoses where it is used are linear IgA dermatosis (bullous dermatosis of childhood), bullous eruption of systemic lupus erythematosus (SLE), erythema elevatum diutinum (EED), bullous pemphigoid, subcorneal pustular dermatosis, IgA pemphigus, urticarial vasculitis (UV), acute febrile neutrophilic dermatosis (Sweet's syndrome), pyoderma gangrenosum, Behçet's syndrome/aphthous stomatitis, rosacea (granulomatous), panniculitis, nodulocystic acne, etc.

Use of dapsone is associated with many pharmacological and idiosyncratic adverse reactions. Common ones are listed in Table 39.1.

Treatment for most cases of CADR associated with dapsone includes immediate withdrawal of dapsone and symptomatic treatment. High-dose systemic corticosteroids for prolonged period is usually needed for DHS. Post-DHS sequel is reported including development of autoantibodies and bullous disorders. Ophthalmological consequences like development of scarring can also occur.[1,5]

COLCHICINE

Colchicine is the active principle of the plant, *Colchicum autumnale.* This alkaloid is commonly used for the treatment of Gout and familial Mediterranean fever. It has antimitotic, anti-inflammatory, and immunosuppressive properties.[6] It is used for dermatological disorders characterized by polymorphonuclear leucocyte (PML) infiltration. Recurrent aphthous stomatitis, Behcet's syndrome, Sweet's syndrome, dermatitis herpetiformis, linear IgA disease, leukocytoclastic vasculitis are among the dermatoses responsive to colchicine apart from gout.[7]

Table 39.1: CADRs due to dapsone

CADRs	Comments
Hypersensitivity reactions Mild Urticaria, FDR (Fig 39.1), maculopapular exanthema (Fig 39.2) and erythema multiforme.	Maculopapular rash develops generally within few hours to 2 days of starting drug and may be self-limiting. Patient needs to be observed for associated signs of systemic involvement like fever, hepatosplenomegaly, eosinophilia, etc. which may point to SCAR
Severe DHS /DRESS[1]	DHS is multiorgan and dose-independent disease. Usually not associated with G-6PD deficiency or methemoglobinemia. Generally starts between 10 days to 6 weeks of starting treatment Patients present with fever, generalized skin eruption, and liver involvement. Other organ involvement including renal may occur in severe cases. Cutaneous eruption range from maculopapular rash to erythema multiforme to toxic epidermal necrolysis. Peripheral eosinophilia and atypical lymphocytes on smear may be present Associated with presence of HLA-B*13:01
SJS/TEN	SJS/TEN is rare but serious side effect of dapsone as with any other sulfa group of drugs.[2]
Exfoliative dermatitis/ Erythroderma	Generalized exfoliative dermatitis with associated signs of erythroderma observed mostly (Fig. 39.3) but not always as part of DHS
Photosensitivity	Usually in context of DHS.[3] Also seen in patients of leprosy and also observed in one patient of linear IgA bullous dermatosis.[1]
Erythema nodosum, oral ulcerations[4]	
Pseudoporphyria[2]	

CADR - cutaneous adverse drug reactions; DHS - dapsone hypersensitivity syndrome; DRESS - drug reaction with eosinophilia and systemic symptoms; FDR - fixed drug reaction; SCAR - severe cutaneous adverse reaction; SJS - Stevens–Johnson syndrome; TEN - toxic epidermal necrolysis.

Fig. 39.1: Fixed drug reaction (FDR) involving hand and lower lip in a patient on dapsone since 3 months for borderline tuberculoid (BT) Hansen.

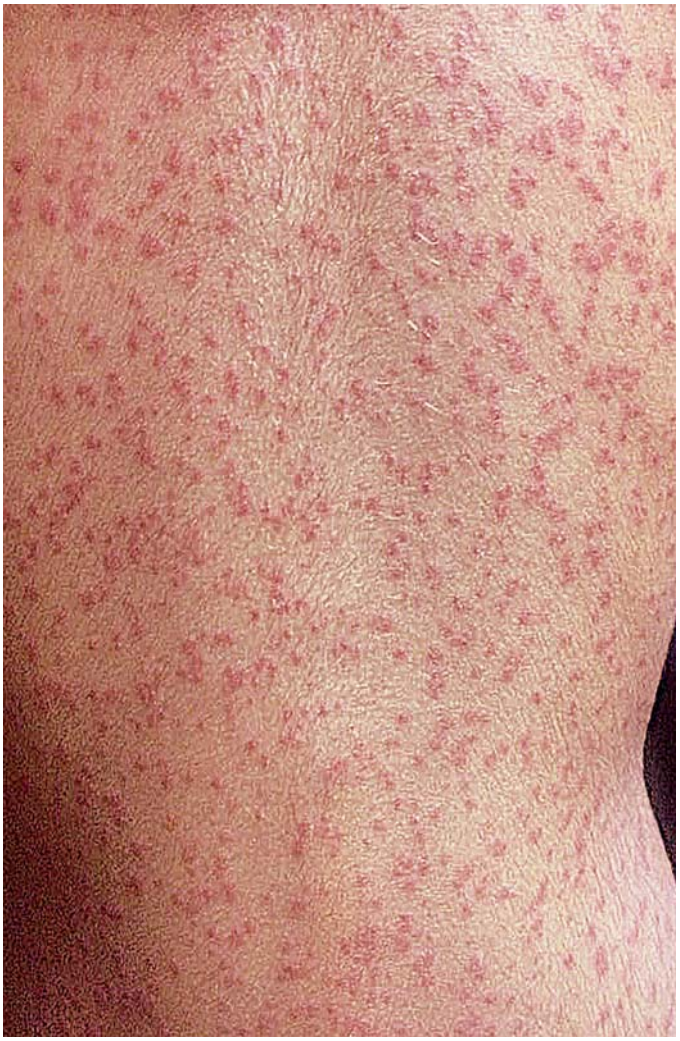


Fig. 39.2: Maculopapular rash over trunk appearing in a patient 36 hours after starting Dapsone for recurrent erythema nodosum.

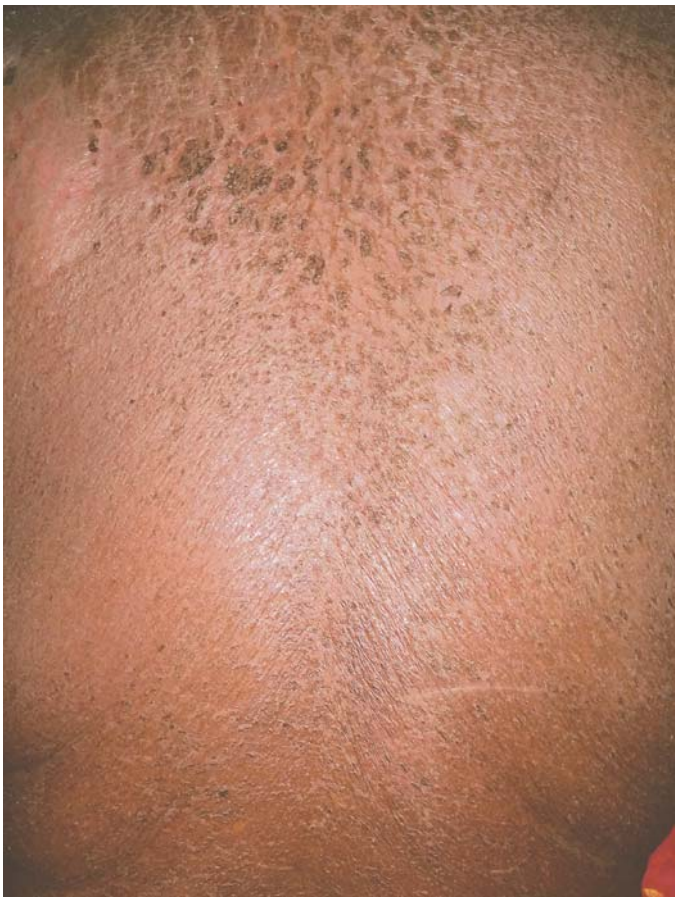


Fig. 39.3: Dapsone hypersensitivity presenting as erythroderma in a 60 year old patient of Borderline leprosy.

Cutaneous side effects of colchicine are uncommon and are listed in Table 39.2.[8–11]

Table 39.2: CADR due to colchicine

Type of CADR	Comments
Alopecia	Both acute overdose and chronic toxicity are associated with diffuse hair loss.
Stomatitis	After acute overdose of drug
Purpura	Due to thrombocytopenia
Urticaria, maculopapular rash, TEN	
Porphyria cutanea tarda	
Lichenoid eruption	
Peripheral neuritis	Burning sensation in skin on chronic use

CADR - cutaneous adverse drug reactions;
TEN - toxic epidermal necrolysis

LEVAMISOLE

Levamisole is an anthelmintic drug belonging to the class of imidazothiazole derivatives with wide range of immunomodulatory actions and has been used for variety of skin disorders such as leprosy, lichen planus, vitiligo, alopecia areata, recalcitrant warts, erythema multiforme, and aphthous ulcers of the mouth either as monotherapy or as an adjunct.[12,13]

Its dermatological side effects are minimal but CADRs have been reported and listed in Table 39.3.[14–18]

Table 39.3: CADR due to levamisole

CADR	Comments
Lichenoid eruptions, alopecia	withdrawal of levamisole in two reported cases led to resolution of lichenoid rash but left behind areas of cicatricial alopecia and hyperpigmented and atrophic lesions in one patient.
Leg ulcers, FDE, and retiform purpura	
Vasculitis/ necrotizing vasculitis	Several cases of vasculitis in children have been reported with use of levamisole. Full-thickness necrosis induced by levamisole vasculitis in patients using cocaine contaminated with levamisole may require multiple excisions and split thickness grafting.

CADR - cutaneous adverse drug reactions;
FDE - fixed drug eruptions.

ANTIMALARIALS: CHLOROQUINE AND HYDROXYCHLOROQUINE

Antimalarials have been used regularly in many autoimmune disorders for their anti-inflammatory as well as immunomodulating effect. Chloroquine (CQ) and hydroxychloroquine (HCQ) are most commonly used molecules while quinacrine (QN) is used occasionally. Off-label dermatological uses of antimalarials include photosensitive dermatoses such as polymorphous light eruption (PMLE), dermatomyositis, sarcoidosis, granuloma annulare (generalized), lymphocytic infiltrate of Jessner, panniculitis (idiopathic), chronic erythema nodosum, and lupus panniculitis.[19,20] Some of the common CADR due to antimalarials are listed in Table 39.4.[4,19,21–23]

A recent report suggests that cutaneous adverse reactions to antimalarials may be more common in patients with dermatomyositis (roughly 30% of patients treated at one center) than in patients with lupus where the reaction rate is roughly 3%–10%.[24]

Table 39.4: CADR due to antimalarials

Dermatoses	Comments
Pigmentary changes Blue-black pigmentation of skin, hair, and nail beds (Fig. 39.4)	Due to deposition of CQ and HCQ in the skin. Seen in 10%–25% patients on long-term CQ or HCQ. Skin pigmentation may darken with ultraviolet exposure and may resolve slowly after withdrawal of medicine.
Slate-grey or yellowish oral pigmentation	Oral pigmentation persists for long time.
Bleaching of hairs of scalp, eyelashes, or eyebrows	
Transverse bands or diffuse pigmentation of nail bed	
Yellowish discoloration of sclera and body secretions mimicking jaundice	Adverse effect of QN which resolves after cessation of medicine.
Pruritus, urticarial, morbilliform rash, exfoliative dermatitis, erythroderma, lichenoid eruption, photosensitivity, and alopecia	All of them resolve on cessation of drug.
AGEP	Many cases reported with HCQ (Fig. 39.5).
Erythema annulare centrifugum	Has been reported with both CQ and HCQ.

AGEP - acute generalized exanthematous pustulosis; CQ - chloroquine; HCQ - hydroxychloroquine; QN - quinacrine.

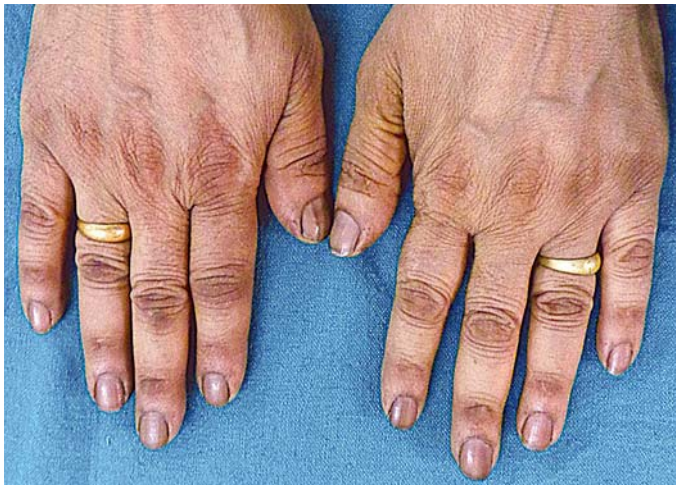


Fig 39.4: Blue black pigmentation of nails in patient of chronic cutaneous discoid lupus erythematosus on hydroxychloroquine for 8 months.

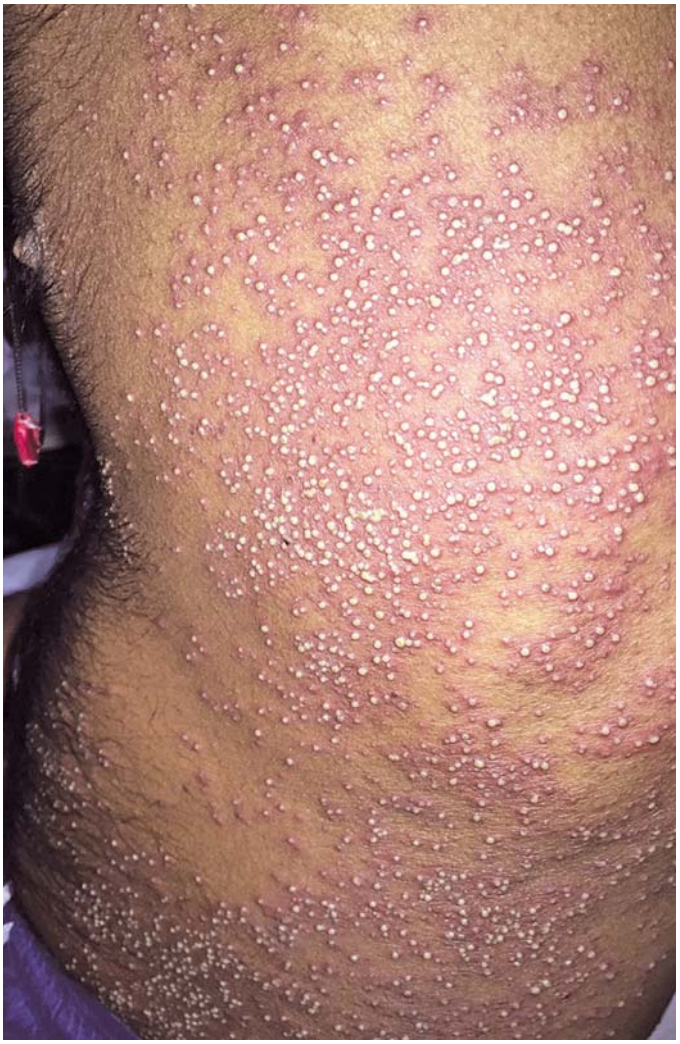


Fig 39.5: Acute generalized exanthematous pustulosis (AGEP) occurring 5 days after starting hydroxychloroquine in a patient of granuloma annulare.

GRISEOFULVIN

An oral antifungal antibiotic, griseofulvin has been found to be useful for many inflammatory disorders including lichen planus and acne vulgaris.[25,26] Potent immunomodulatory properties of griseofulvin has been associated with its mechanism of action as an microtubule antagonist.[27] Griseofulvin is known to produce cutaneous adverse reactions including the following[2,28]:

- Urticaria (Fig. 39.6), flushing, skin rashes
- Lichenoid eruptions
- Photosensitivity
- Drug-induced lupus erythematosus (Fig. 39.7)

TETRACYCLINE

Tetracycline is a common broad spectrum antibiotic used effectively for several decades by physicians for

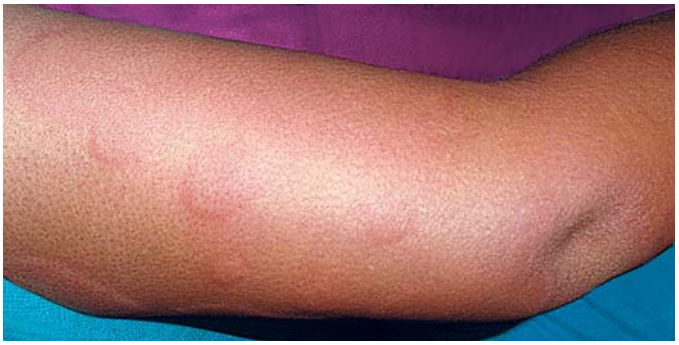
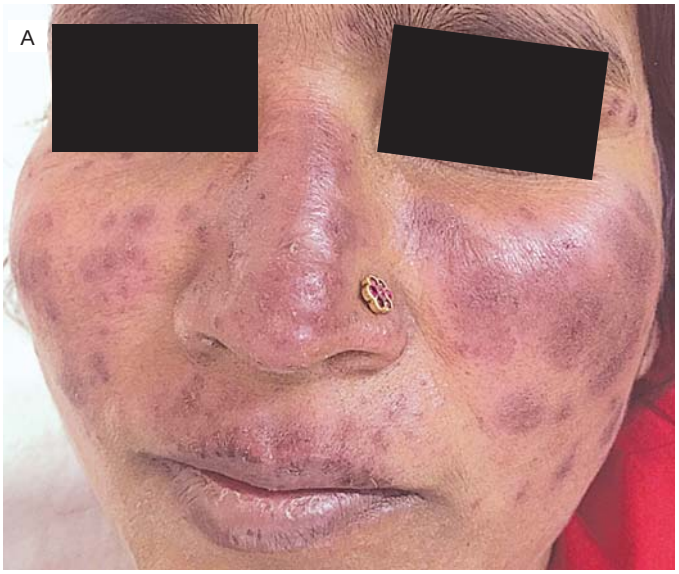


Fig 39.6: Urticarial rash appearing in a patient of Tinea corporis 10 days after starting her on griseofulvin.



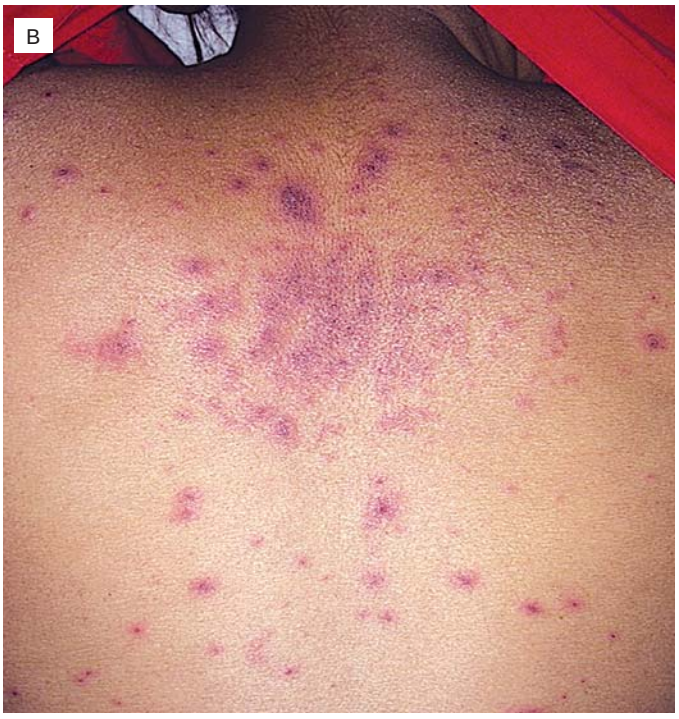


Fig 39.7: Lupus erythematosus like eruptions over; (A) butterfly area of face and (B) trunk appearing 6 weeks after griseofulvin therapy in a patient of tinea corporis.

various infective disorders before newer generation antibiotics became available. Among dermatologists this group of drugs are still widely used for acne and several sexually transmitted diseases. Due to its immunomodulatory and anti-inflammatory effect, it has been found to be useful for autoimmune vesiculobullous disorders, rosacea, sarcoidosis, panniculitis, confluent and reticulate papillomatosis (CRP), oral lichen planus and others. Details regarding CADR reported with tetracyclines are covered in Chapter 33. Briefly the reported CADR are listed below[2]:

- Exanthematous rash
- Erythema multiforme
- Serum sickness-like illness
- Discoid lupus erythematosus (DLE)/SLE
- Vasculitis
- AGEP
- DHS/DRESS, SJS/TEN
- FDE
- Pseudoporphyria
- Photosensitivity/phototoxicity, photoonycholysis
- Dyspigmentation
- Lichenoid eruption

GOLD

It is rarely used now but in dermatology it is considered as secondary option in the treatment of disorders such as discoid and systemic lupus erythematosus, psoriatic arthritis, bullous dermatoses like pemphigus vulgaris, cicatricial pemphigoid and epidermolysis bullosa acquisita (EBA).

Incidence of adverse effects is higher with parental gold therapy (40%) as compared to oral salt (10%–30%).[6] CADR associated with use of Gold are listed in Table 39.5.[2,6,29,30]

THALIDOMIDE

Thalidomide has been used in various dermatological diseases for its effect as an immunomodulator and anti-inflammatory drug. As an immunomodulator, it is very effective in leprosy for erythema nodosum leprosum (ENL)/type 2 lepra reaction and also in diseases such as sarcoidosis, chronic graft-versus-host disease, erosive lichen planus, autoimmune vesiculobullous diseases and others.[6] CADR related to thalidomide are mentioned in Table 39.6.[31]

Table 39.5: CADR due to gold therapy

CADR	Comments
Lichen planus–like and pityriasis rosea–like skin rashes (Fig. 39.8)	May persist for several months after therapy is discontinued
Cheilitis, stomatitis, metallic taste	
Generalized eczematous dermatitis (Fig. 39.9)	When significant dermatitis occurs, therapy should be withheld
Alteration in pigmentation of oral mucosa	Due to deposition of metal in mucosa
Eosinophilia and pruritus	

CADR - cutaneous adverse drug reactions.

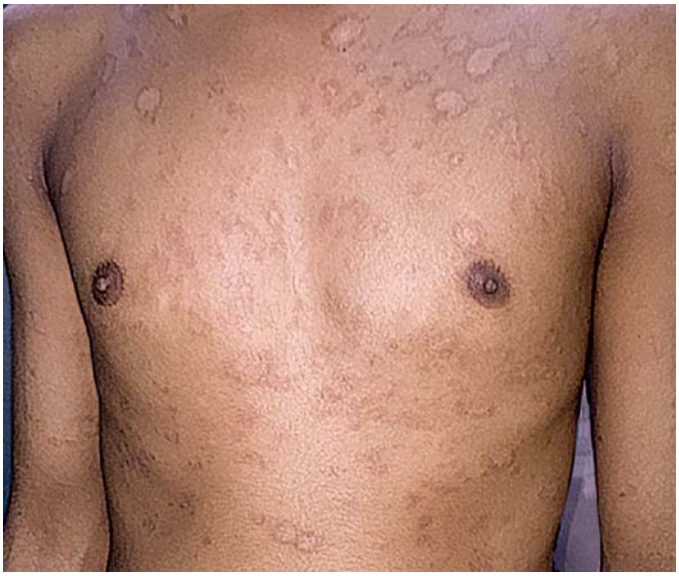


Fig 39.8: Multiple annular lesions simulating pityriasis rosea appearing in a patient on gold therapy for psoriatic arthritis.

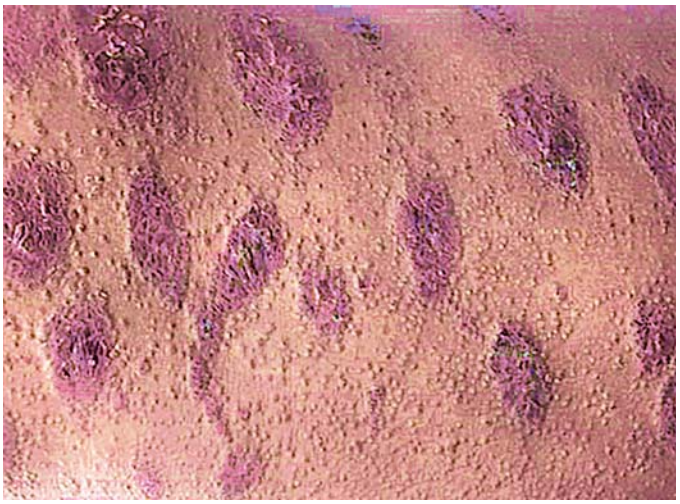


Fig 39.9: Extensive violaceous discoid dermatitic plaques with scattered papular lesions in a patient of rheumatoid arthritis appearing 2 months after injectable gold therapy.

Table 39.6: CADR due to thalidomide

CADR	Comments
Xerostomia, brittle finger nails, erythema of palms, xerosis and pruritus.	Mild and do not call for drug withdrawal
Exfoliative dermatitis, erythroderma, allergic vasculitis, thrombocytopenic purpura, TEN	Severe adverse effects and require stopping of drug
Exacerbation of psoriasis	

CADR - cutaneous adverse drug reactions; TEN - toxic epidermal necrolysis.

LEARNING ESSENTIALS

- It is crucial to identify subtle signs of serious CADR at the earliest to prevent long-term consequences.
- Frequently used drugs like dapsone, CQ are generally considered as safe molecules but idiosyncratic drug reactions should always be kept in mind and should be recognized at an early stage to avoid life threatening situations.
- For drugs like thalidomide, teratogenicity is most feared side-effect but frequent occurrence of other ADRs should also be kept in mind.
- Lichen planus–like rash is also common with many drugs which can complicate patient's existing situation and may sometime lead to diagnostic dilemma.

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Chapter

40

Cutaneous Adverse Drug Reactions to Chemotherapeutic Agents

Rashmi Sarkar • Pooja Arora

SUMMARY

Chemotherapeutic agents may be associated with a variety of cutaneous adverse effects that may range from benign conditions to life-threatening reactions. It is important for the treating physician to distinguish these reactions from other cutaneous disorders seen in cancer patients which can be infections, nutritional deficiency, reactions due to concurrent radiotherapy, graft versus host disease, cutaneous metastases.

Alopecia, hyperpigmentation, nail dystrophy, and mucositis are the common adverse effects seen with anti-cancer drugs. The unusual side effects include extravasation, autoimmune phenomenon, acral erythema, neutrophilic eccrine hidradenitis, radiation recall, and enhancement. In rare cases, these drugs may cause hypersensitivity reaction that may warrant immediate management including withdrawal of offending drug.

INTRODUCTION

Chemotherapy is an important part of treatment of cancers. Chemotherapeutic agents can cause a variety of adverse effects of which mucocutaneous side effects are quite common. It is important to recognize these reactions as they may require alterations in management including discontinuation of causative drug.

Box 40.1 depicts the various cutaneous adverse drug reactions (CADRs) that can occur with chemotherapeutic agents.

Box 40.1: Cutaneous adverse drug reactions

Hyperpigmentation
Alopecia
Acral erythema
Acneiform eruptions
Nail changes
Neutrophilic eccrine hidradenitis
Eccrine squamous syringometaplasia
Mucositis
Extravasation
Autoimmune phenomenon
Flushing
Radiation recall
Radiation enhancement
Interaction with UV light
Photo-onycholysis
UV recall reaction
Xerosis
Morbilliform drug eruptions
Hypersensitivity
Inflammation of actinic keratoses
Unique drug-specific reactions

UV - ultraviolet.

HYPERPIGMENTATION

It is a common cutaneous side effect of chemotherapeutic agents. It has varied manifestations and besides skin (Figs. 40.1, 40.2 and 40.3) it can affect the nails (Figs. 40.4, 40.5 and 40.6) and mucous membranes also (Figs. 40.7 and 40.8). The involvement can be localized or diffuse.

Pathogenesis

Various mechanisms for chemotherapy-induced pigmentation have been described. The exact mechanism may vary depending on the drug.

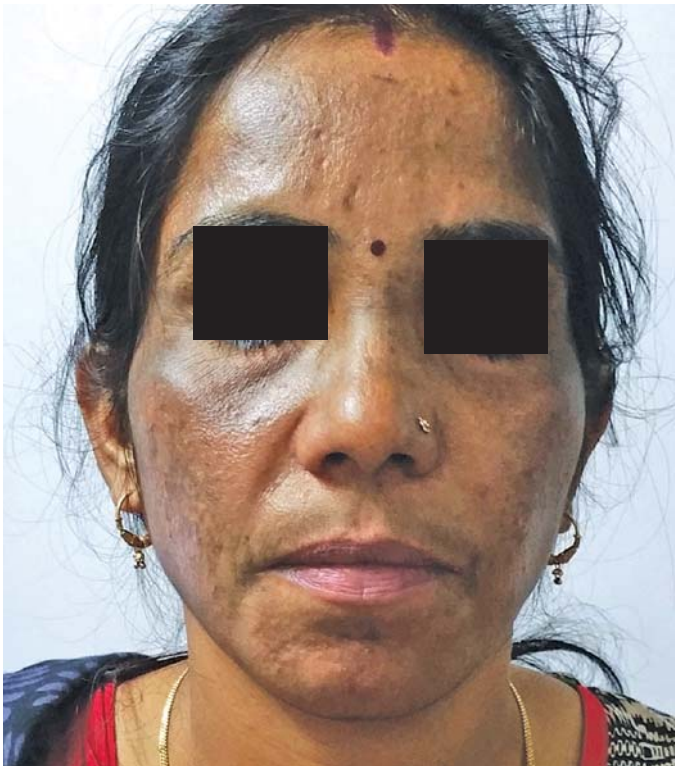

Fig. 40.1: Facial pigmentation in a patient on cyclophosphamide.

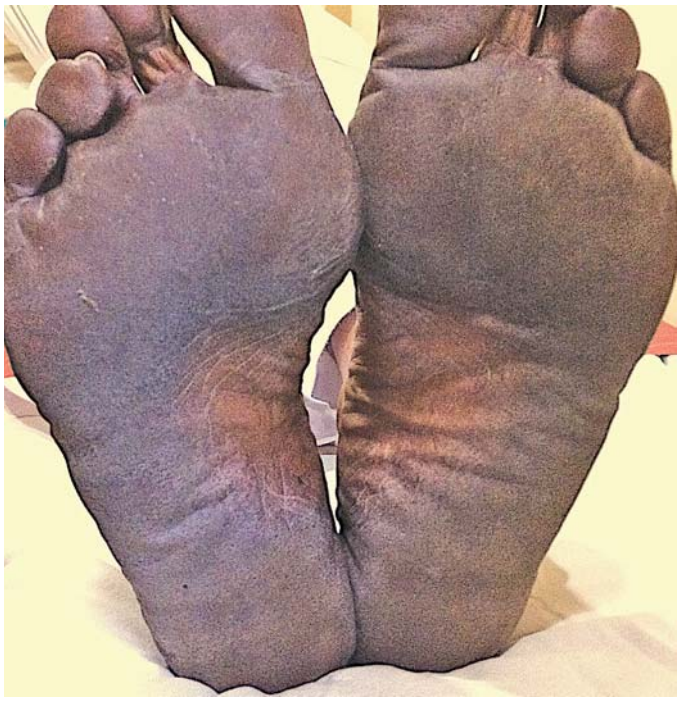

Fig. 40.2: Pigmentation on soles due to busulfan in a patient with chronic myelogenous leukemia.

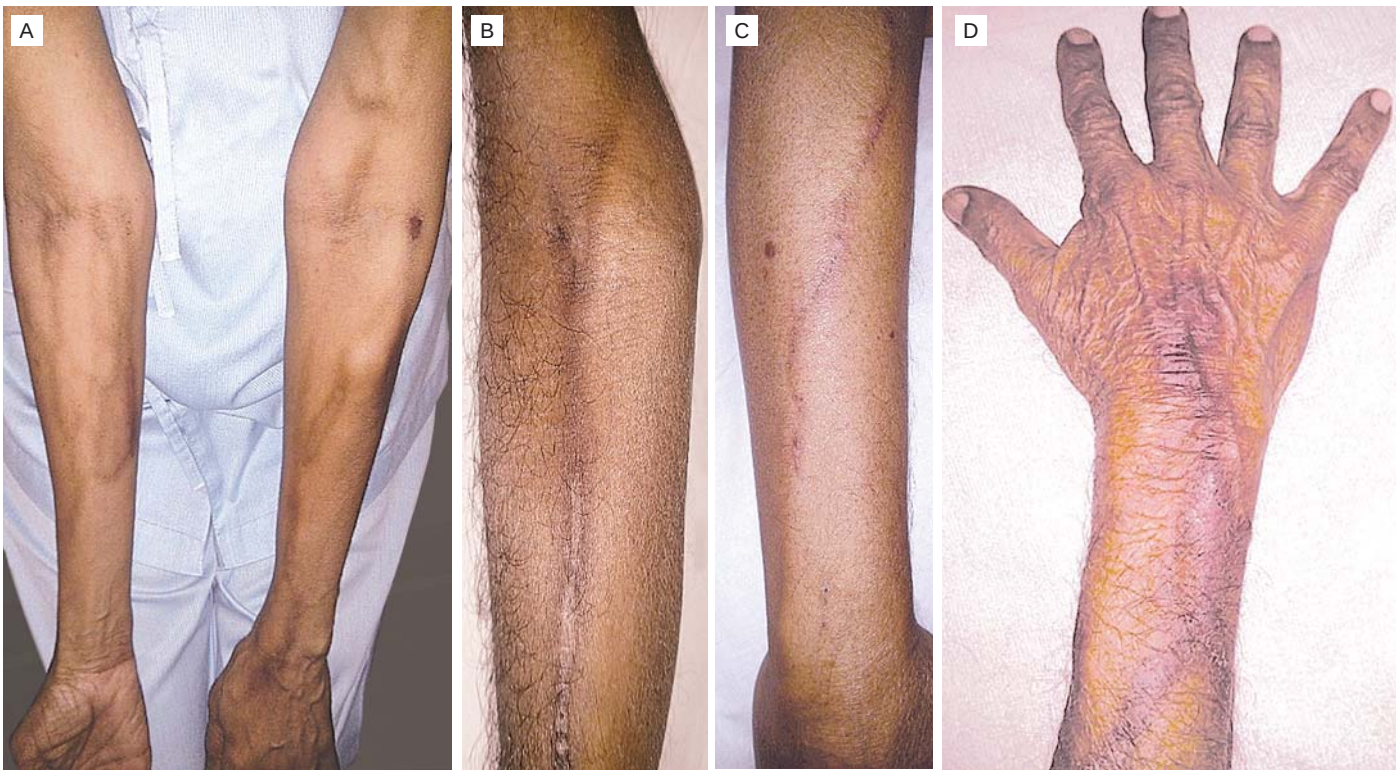

Fig. 40.3: (A–D) Serpentine supravenous pigmentation in two patients- one on Docetaxel, cisplatin, fluorouracil (DCF) regimen for squamous cell carcinoma, mid-esophagus; other on folinic acid, 5-fluorouracil, oxaliplatin (FOLFOX) regimen for adenocarcinoma colon. (Courtesy of Dr. Grishma Gandhi, Mumbai.)

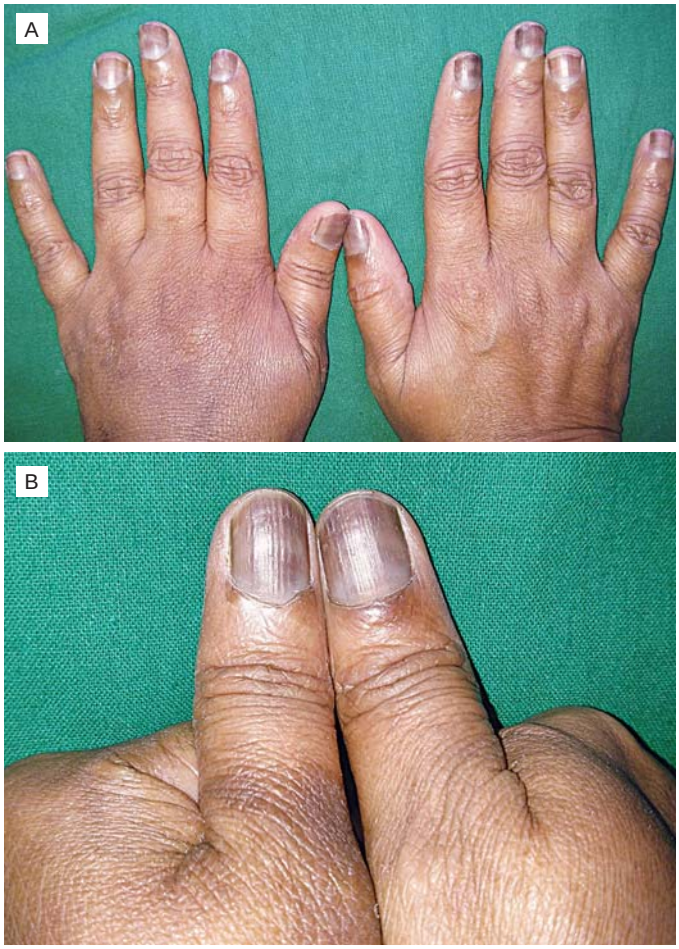

Fig. 40.4: (A & B) Diffuse nail pigmentation due to cyclophosphamide in a patient on 5-FU, epirubicin, cyclophosphamide (FEC) regimen for carcinoma breast. (Courtesy of Dr. Grishma Gandhi, Mumbai.)

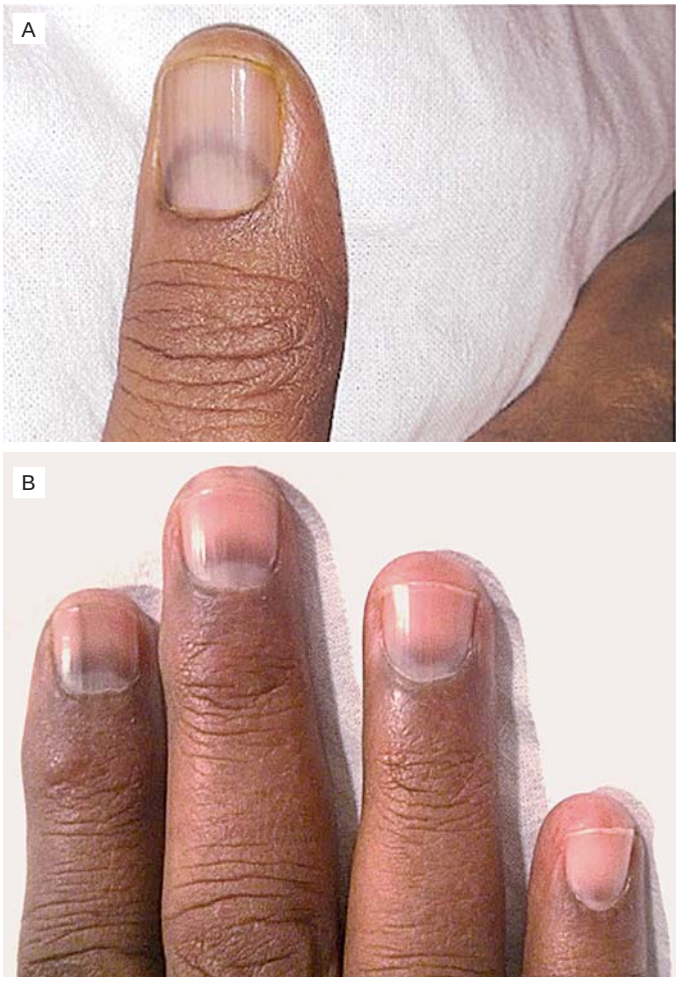

Fig. 40.6: (A & B) Transverse band in a patient on Adriamycin, cyclophosphamide (AC) regimen for carcinoma breast. (Courtesy of Dr. Grishma Gandhi, Mumbai.)

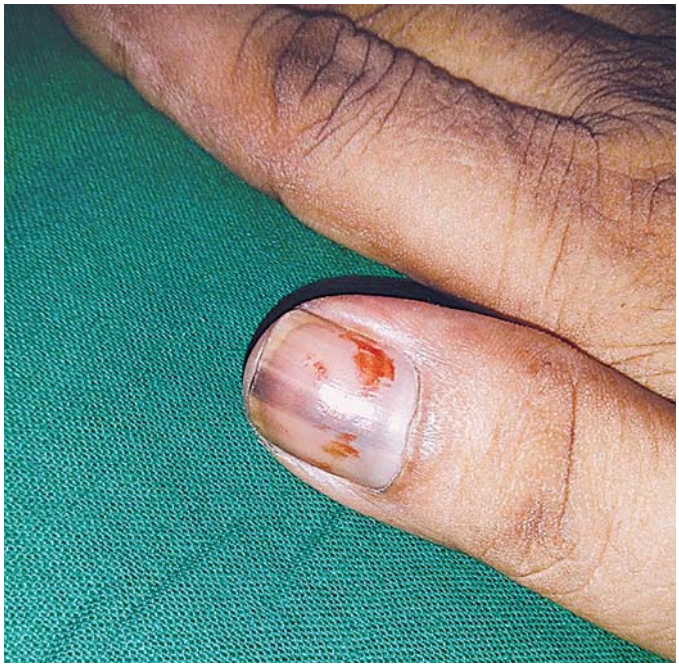

Fig. 40.5: Longitudinal melanonychia due to cyclophosphamide. (Courtesy of Dr. Grishma Gandhi, Mumbai.)

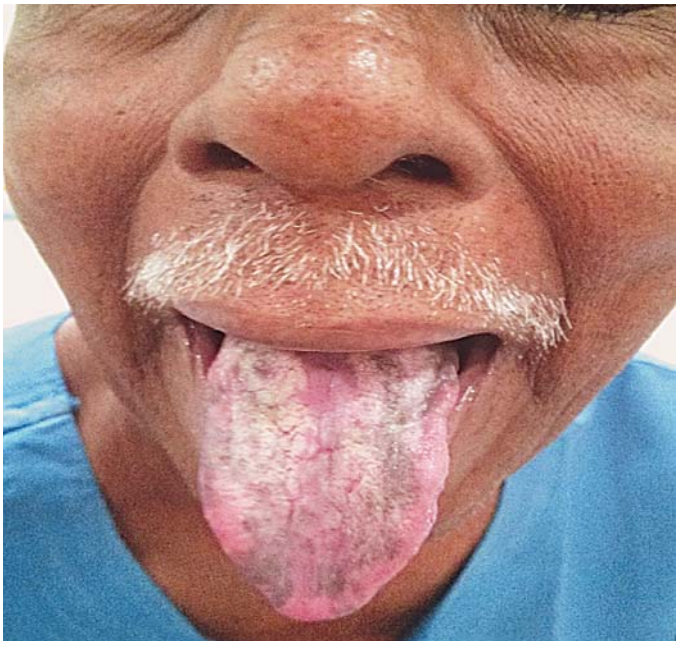

Fig. 40.7: Pigmentation on tongue in a patient on Folinic acid, 5-fluorouracil, oxaliplatin (FOLFOX) regimen for carcinoma colon. (Courtesy of Dr. Grishma Gandhi, Mumbai.)

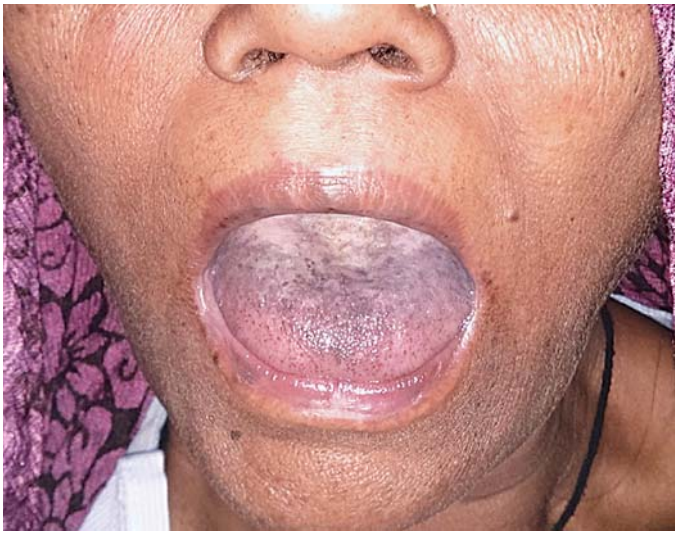

Fig. 40.8: Tongue pigmentation due to cyclophosphamide in a patient of carcinoma breast. (Courtesy of Dr. Grishma Gandhi, Mumbai.)

1. Direct skin toxicity due to secretion of the drug in sweat leading to accumulation in skin.
2. Increased blood flow leading to deposition of the drug in certain areas.
3. Depletion of tyrosinase inhibitors.
4. Suppressed adrenal function leading to increased adrenocorticotropic hormone (ACTH) and melanocyte-stimulating hormone (MSH).
5. Direct effect on melanocytes leading to increased melanin production.

Histology

There is increase in melanocytes at dermoepidermal junction accompanied by melanophages in the papillary dermis. Sparse perivascular lymphocytic infiltrate may also be present in the dermis.

Causative agents and the characteristic pattern of hyperpigmentation[1] have been described in Table 40.1.

Course and Treatment

Hyperpigmentation generally resolves with withdrawal of chemotherapeutic agent. Sun protection in the form of sunscreens may be prescribed to halt progression. Drug-induced hyperpigmented bands on nails grow out after 6 months.[2] However, pigmentation over teeth is permanent.

ALOPECIA

It is the most common cutaneous adverse reaction to chemotherapeutic agents. It usually manifests as anagen effluvium, which occurs due to interruption

Table 40.1: Causative agents and the characteristic pattern of hyperpigmentation

Drug	Pattern
Cyclophosphamide	Localized (palms, soles) or generalized transverse bands or diffuse hyperpigmentation of nails, teeth, mucosa. Hair color may change from light red to black.
Cisplatin	Usually causes localized hyperpigmentation over extensor aspect of extremities, elbows, knees, neck, sites of pressure; hair may change color.
Busulfan	Generalized dusky hyperpigmentation that resembles Addisonian pigmentation on extensor aspect of extremities, elbows, knees, neck, sites of pressure; hair may change color.
Fluorouracil	i. Serpentine supravenous hyperpigmentation characterized by streaks of hyperpigmentation extending from shoulder to hands. ii. Pigmentation on sun exposed areas. iii. Reticulate hyperpigmentation that can be widespread. iv. Localized hyperpigmentation-transverse bands over joints, diffuse hyperpigmentation or macular hyperpigmentation over palms. v. Hyperpigmentation of nails.
Bleomycin	i. Flagellate hyperpigmentation (Fig. 40.9), characterized by band like streaks of hyper pigmentation, over trunk and proximal extremities and sites of trauma. ii. Localized hyperpigmentation over pressure areas, palmar crease and striae.
Methotrexate	i. Generalized brownish hyperpigmentation that may be more pronounced over sun exposed areas. ii. Flag sign: Hyperpigmented bands on hair, alternating with normal colored hair.
Dactinomycin	Diffuse hyperpigmentation.
Daunorubicin	Hyperpigmentation over sun exposed areas.
Hydroxyurea	Generalized hyperpigmentation that is more pronounced on face, neck, lower arms, sites of pressure.
Procarbazine	Diffuse hyperpigmentation.
Vinca alkaloids	Localized hyperpigmentation.
Thiotepa	Hyperpigmentation in occluded areas, leukoderma may occur.
Paclitaxel	Localized hyperpigmentation.
Etoposide	Hyperpigmentation of occluded areas.

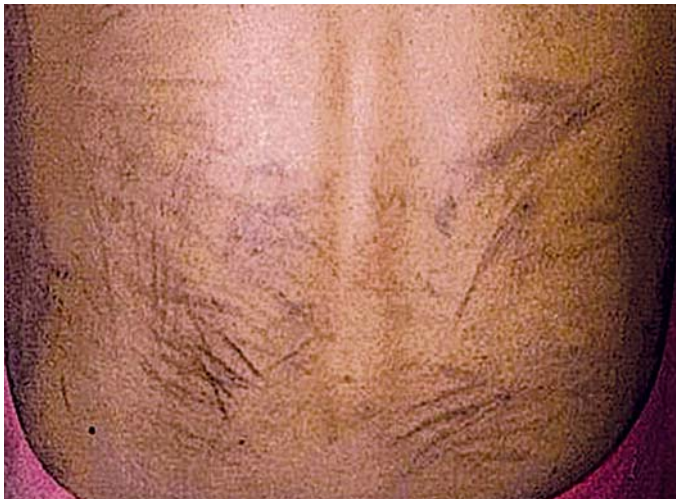

Fig. 40.9: Flagellate pigmentation due to bleomycin in a patient of testicular tumor. (Courtesy of Dr. R.D. Mehta, Bikaner.)

of mitotic activity in the hair matrix cells that are rapidly dividing. This leads to cessation of hair shaft formation or produces a weakened hair shaft that is prone to breakage.

Clinical Manifestation

Anagen effluvium manifests as sudden diffuse hair loss (Fig. 40.10) that starts within 7-10 days of initiation of chemotherapy and peaks around 2 months. Hair in the resting phase are spared leading to incomplete hair loss which may become complete with repeated exposures. Long-term therapy can also affect anagen hair in other body parts.[3]

Course

Chemotherapy-induced hair loss is usually reversible after cessation of drug. However, the hair color or texture may change. The pathogenesis of this effect is not completely understood.

Management

Scalp hypothermia has been tried but with limited success. It works by inducing vasoconstriction that decreases the amount of drug reaching the follicles and also lowers the metabolic rate and hence the drug uptake. It is currently not recommended.[4] Scalp tourniquet has also been used and it decreases the scalp blood flow.

ImuVert, an immunomodulator that induces production of interleukin (IL)-1, has been tried in animal models. It was found to reduce alopecia due to cytarabine and doxorubicin.[5,6]

Minoxidil has been tried with limited success.

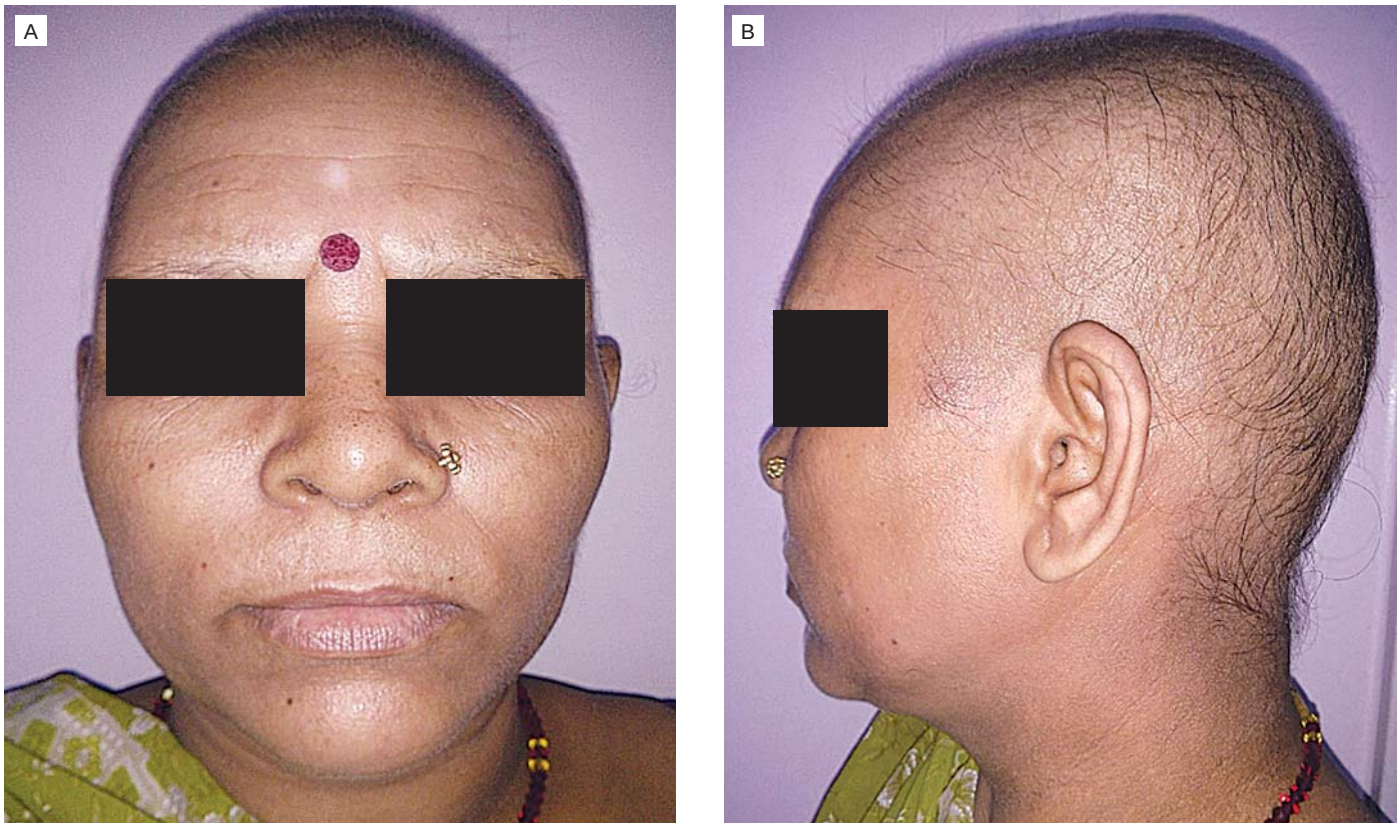

Fig. 40.10: (A & B) Alopecia due to 5-FU, epirubicin, cyclophosphamide (FEC) regimen in a patient of carcinoma breast. (Courtesy of Dr. Grishma Gandhi, Mumbai.)

ACRAL ERYTHEMA

It is also known as Hand-Foot syndrome.

Clinical Features

The eruption may be preceded by a prodrome of tingling or burning sensation which is followed by appearance of edema and well-defined erythematous plaques (Figs. 40.11) that are associated with pain. Hands are usually more severely affected. Blistering and superficial desquamation may occur.

Pathophysiology

The pathogenesis is poorly understood. It has been hypothesized that the chemotherapeutic agent may accumulate in the acral regions and cause direct toxic effects on the skin.

Histopathology

The condition is characterized by epidermal spongiosis, vacuolar change in the basal layer with apoptotic keratinocytes. The dermis contains perivascular lymphocytic infiltrate.

Causative Drugs

Chemotherapeutic agents associated with acral erythema (AE) are listed in Box 40.2.

Box 40.2: Chemotherapeutic agents associated with acral erythema

- **Most common**
  - 5-Fluorouracil
  - Doxorubicin
  - Cytarabine
- **Less common**
  - Cisplatin
  - Hydroxyurea
  - Methotrexate
  - Sorafenib
  - Sunitinib

Course

AE is a dose-related adverse effect, hence dose reductions may improve symptoms. Lesions resolve within weeks of withdrawal of drug.

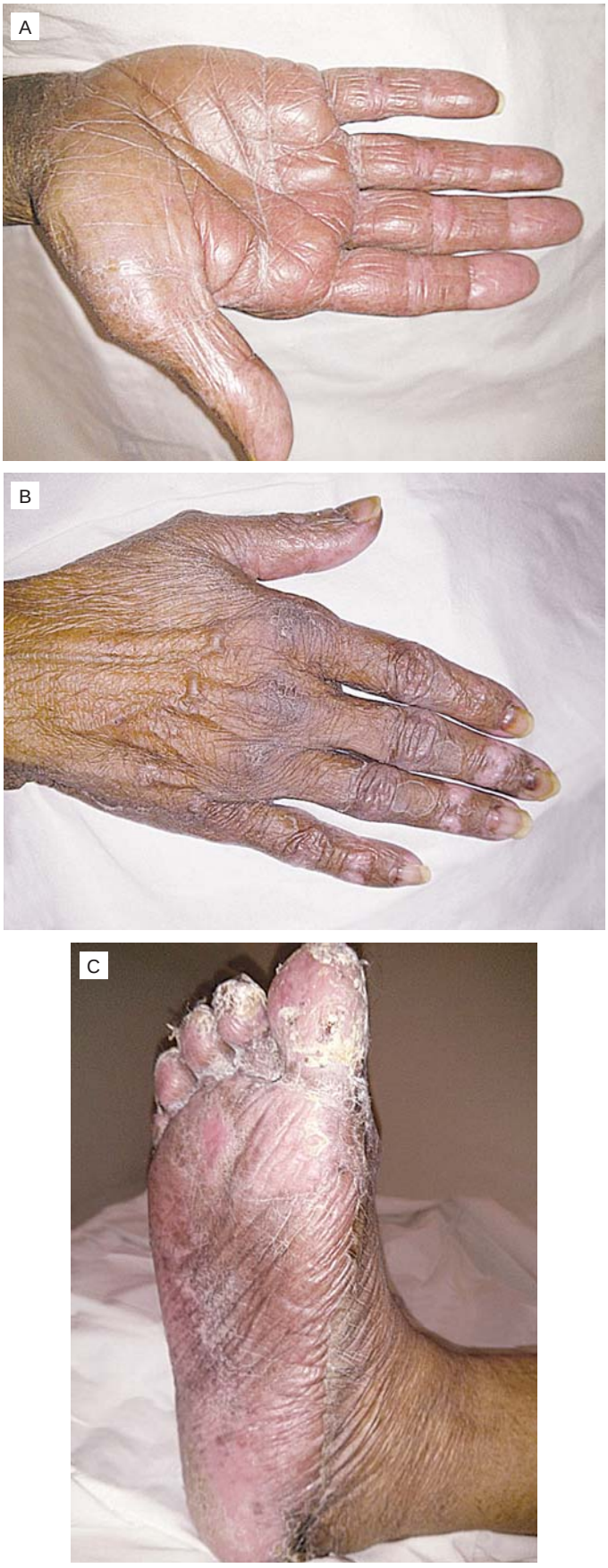

Fig. 40.11: (A–C) Hand foot syndrome due to docetaxel in a patient of metastatic breast cancer. (Courtesy of Dr. Grishma Gandhi, Mumbai.)

Treatment

Application of ice water to the acral areas decreases the blood flow and hence may prevent the reaction. Symptomatic treatment to reduce pain and edema and prevent infection can be given. Systemic corticosteroids may be beneficial. Pyridoxine (vitamin B6) in a dose of 100 mg/day to reduce pain and edema and prevent infection can be given.[7]

ACNEIFORM ERUPTIONS

Causative Agents

Causative agents include epidermal growth factor receptor (EGFR) inhibitors such as gefitinib, cetuximab.

Pathogenesis

Various theories have been postulated for chemotherapy-induced acneiform eruptions.

1. Excessive follicular hyperkeratosis causing plugging and obstruction subsequently leading to rupture of the follicle wall with chemotaxis of inflammatory mediators.
2. Direct effect on keratinocytes.

Clinical Features

It is characterized by erythematous papules, sterile pustules on an erythematous base (Figs. 40.12 and 40.13).

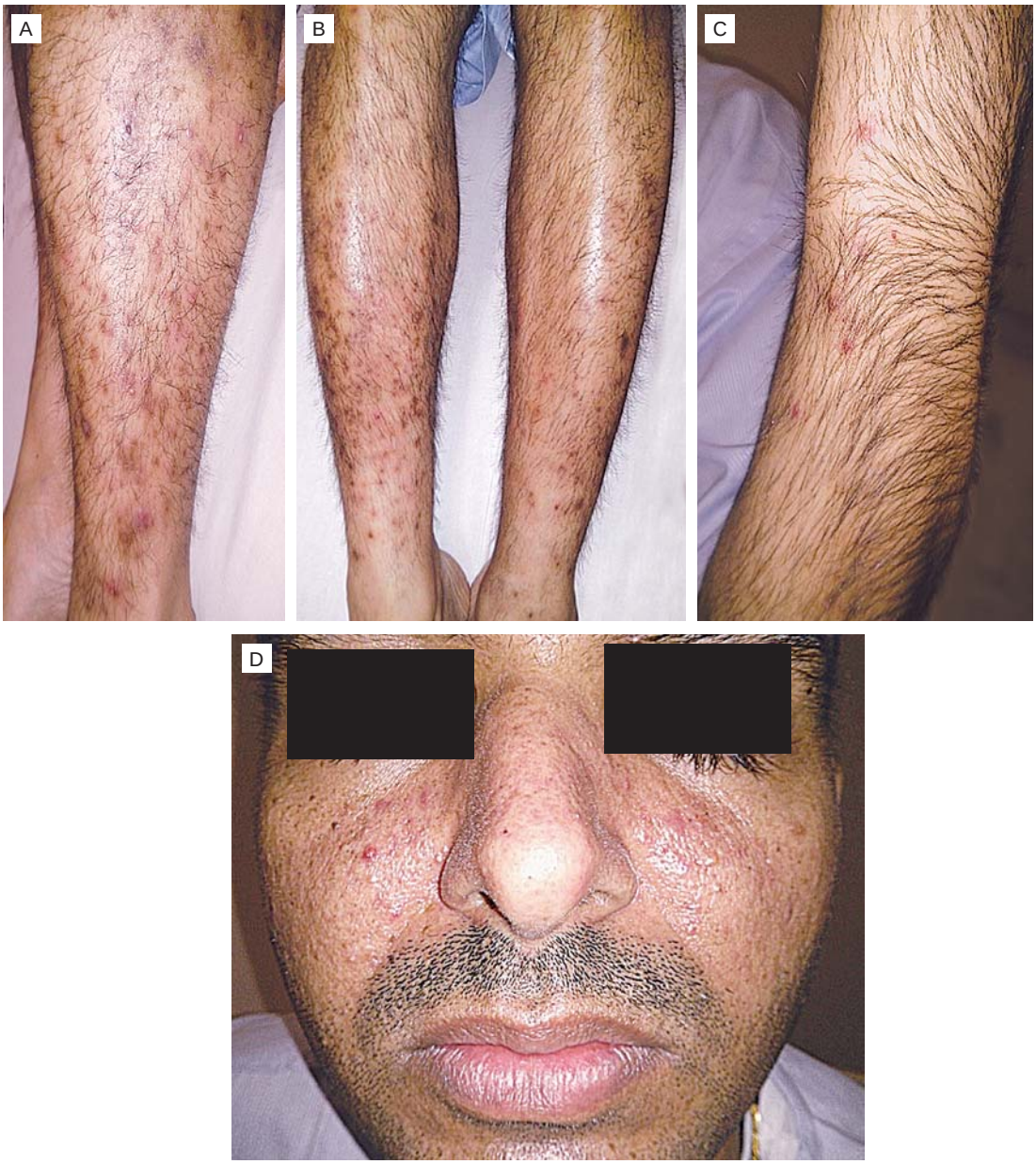

Fig. 40.12: (A–D) Papulopustules and xerosis secondary to EGFR inhibitors. (Courtesy of Dr. Grishma Gandhi, Mumbai.)

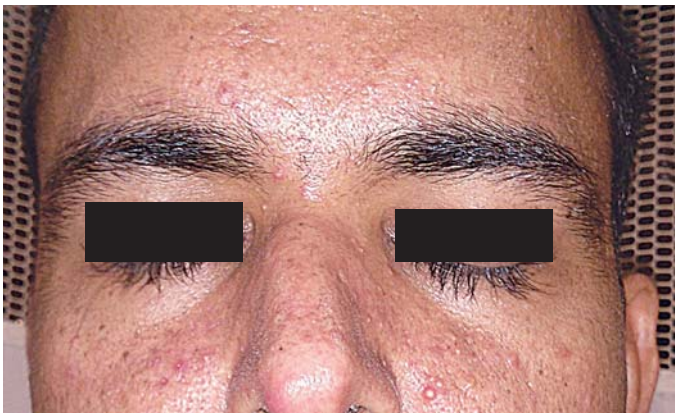

Fig. 40.13: Papulopustules, trichomegaly and thick dense eyebrows secondary to EGFR inhibitors. (Courtesy of Dr. Grishma Gandhi, Mumbai.)

Course

It can occur as early as 1 week after starting the treatment.

Treatment

Oral tetracyclines, topical retinoids, and benzoyl peroxide may be used for treatment.

NAIL CHANGES

Various nail changes associated with chemotherapeutic agents are depicted in Table 40.2.

Table 40.2: Various nail changes associated with chemotherapeutic agents

	Manifestation	Causative agent	Comment
1	Nail Hyperpigmentation	Doxorubicin 5-Fluorouracil Cyclophosphamide	
2	Transverse leukonychia	Doxorubicin Vincristine Docetaxel Cyclophosphamide	Due to transient cessation of growth of the nail plate
3	Onycholysis	Doxorubicin Paclitaxel	Resolves with cessation of drug
4	Paronychia Pyogenic granuloma	EGFRI	Inhibition of nail matrix keratinocytes

EGFRI - epidermal growth factor receptor inhibitor.

NEUTROPHILIC ECCRINE HIDRADENITIS

It is also known as drug-induced eccrine hidradenitis.

Clinical Features

Neutrophilic eccrine hidradenitis (NEH) is characterized by the appearance of erythematous papules, nodules, pustules or plaques on the head, neck, trunk or extremities accompanied with fever. The lesions may be purpuric or hyperpigmented and are usually asymptomatic. Rash resolves with desquamation without any scarring or hyperpigmentation.

Histopathology

The histopathology is classical and is characterized by dense neutrophilic infiltrate in and around the eccrine glands with necrosis of eccrine epithelial cells. Other findings include dermal edema, epidermal spongiosis, squamous syringometaplasia and keratinocyte necrosis.[8]

Pathogenesis

Mechanism remains unclear. It could be due to the direct toxic effect of the chemotherapeutic agent on the eccrine glands due to higher concentration in the sweat. Direct neutrophilic effect is unlikely as there are few case reports where NEH has been described in neutropenic patients in the absence of neutrophils on biopsy.

Course and Treatment

It is a self-limiting disorder hence does not require treatment. It resolves in 2-3 weeks. Corticosteroids and dapsone have been tried with variable success but their efficacy is uncertain.[9,10]

ECCRINE SQUAMOUS SYRINGOMETAPLASIA

It clinically resembles NEH and may be considered the noninflammatory end of the spectrum of chemotherapy-induced eccrine gland reactions.[8]

Causative Agents

These are depicted in Box 40.3.

It occurs days after starting treatment & clears spontaneously within 4 weeks.

Box 40.3: Causative agents

- Cytarabine
- Daunorubicin
- Cisplatin
- 5-Fluorouracil
- Doxorubicin
- Cyclophosphamide
- Methotrexate
- Etoposide
- Melphalan
- Suramin
- Thiotepa

Histopathology

The classical feature is squamous metaplasia of eccrine glands in the papillary dermis. Neutrophilic infiltrate is absent.

MUCOSITIS

It is a common adverse effect of chemotherapeutic agents. The most frequent causative agents are bleomycin, methotrexate, daunorubicin, docetaxel, 5-fluorouracil and dactinomycin.

Clinical Features

Chemotherapy-induced mucositis is characterized by painful erosions and ulcers over the non-keratinized mucosa. These may become confluent later. The changes usually occur within 4 -7 days of start of chemotherapy.

Pathogenesis

The oral epithelial cells are rapidly dividing and hence are susceptible to the effects of chemotherapy. The latter slows down the renewal rate of basal cells leading to atrophy and hence erosions. Mucositis is dose dependent. Various factors associated with higher risk include young age, pre-existing oral disease, poor oral hygiene, the agent used and its total dose, type of drug delivery, impaired renal or liver function and simultaneous radiotherapy.

Treatment

Mucositis is treated symptomatically with topical coating agents, anesthetic agents and pain killers. Patients on anti-cancer drugs are prone to infections hence should be monitored for signs of secondary infection.

Prevention

An oral cooling using ice chips induces vasoconstriction and can be used to prevent mucositis. Other agents that have been used but lack data are allopurinol, β-carotene, granulocyte colony stimulating factor (G-CSF), palifermin.[11]

Course

Lesions resolve within 2 weeks of withdrawal of the drug.

EXTRAVASATION

Chemotherapeutic agent can escape from a vessel to the surrounding tissue. This is called as extravasation and may occur due to leakage or by direct infiltration. The incidence of this adverse effect is estimated to be 0.1%.

Pathogenesis

Based on the potential for toxicity, chemotherapeutic agents can be classified as vesicants or irritants. Irritants induce inflammation without tissue necrosis. This is manifested as erythema, pain or phlebitis, hyperpigmentation and tenderness. There are usually no sequelae. A vesicant usually causes tissue necrosis due to extravasation.

Clinical Features

These include burning, erythema, edema (Fig. 40.14) that progresses on to discoloration, induration, or blistering. Necrosis with ulceration and eschar formation may follow. This can lead to complications if untreated.

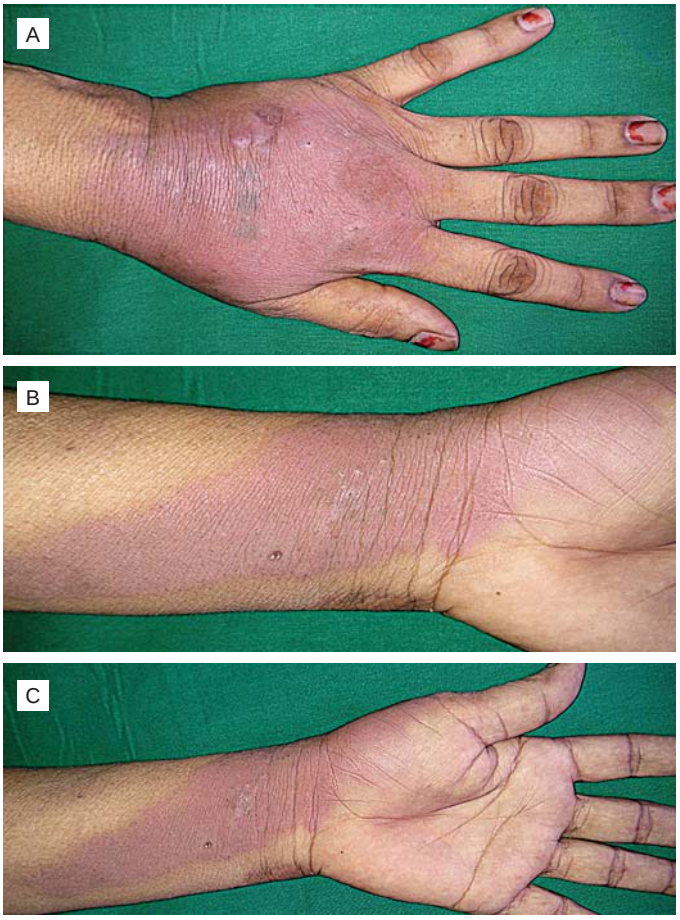

Fig. 40.14: (A–C) Irritant extravasation reaction due to docetaxel in a patient on docetaxel and cyclophosphamide for carcinoma breast. (Courtesy of Dr. Grishma Gandhi, Mumbai.)

Causative Agents

Causative agents include vincristine, doxorubicin, actinomycin D, bleomycin, vinblastine, etoposide, cisplatin and docetaxel.

Management

1. Discontinue infusion
2. Aspirate residual drug
3. Elevation of extremity
4. Application of heat or cold
5. Antidotes: Topical dimethyl sulfoxide (DMSO) for anthracycline or mitomycin extravasation has been used. Hyaluronidase has been used for extravasation of vinca alkaloid and etoposide.
6. Debridement

AUTOIMMUNE PHENOMENON

These have been depicted in Table 40.3.

Table 40.3: Autoimmune phenomenon

Manifestation	Causative drug	Remark	Treatment
Cutaneous atrophy	5-Fluorouracil	Resolves on discontinuation	Fillers may be used
Scleroderma-like reaction	Bleomycin		
Raynaud's phenomenon	Bleomycin		
SLE & DM-like eruption	Hydroxyurea	Muscle inflammation, secondary malignancy are not seen	Sun protection, topical steroids

SLE - systemic lupus erythematosus;
DM - dermatomyositis.

FLUSHING

Drugs associated with flushing are depicted in Box 40.4.

Box 40.4: Drugs associated with flushing

Asparaginase
Etoposide
Bleomycin
5-Fluorouracil
Cisplatin
Paclitaxel
Cyclophosphamide
Procarbazine
Docetaxel
Tamoxifen
Doxorubicin
Suramin

Mechanism

The agent may act on the autonomic nervous system (ANS) to exert transient vasodilation or directly affect the vascular smooth muscle. ANS also supplies the eccrine glands. Hence, sweating may occur in cases by former mechanism.

RADIATION RECALL

A previously irradiated site may become inflamed on administration of a chemotherapeutic agent. This is known as radiation recall.

Causative Agents

Causative agents include doxorubicin, dactinomycin, hydroxyurea, methotrexate, etoposide, vinblastine, 5-fluorouracil, melphalan, cyclophosphamide, cytarabine.

Clinical Features

The reaction can occur within days to years of radiation therapy but generally occurs within hours to days. It is characterized by erythema, desquamation, edema and vesiculation with or without pain or ulceration. The lesions correspond to the site of previous radiotherapy. The reaction is usually cutaneous but in rare cases organ involvement may occur. There are several factors that affect the severity of reaction.

1. Period between radiotherapy and chemotherapy: Short interval correlates with severe radiation recall reactions.
2. Dose of irradiation used: Higher dose correlates with severe reactions.

Pathogenesis

Various hypothesis have been put forth.

1. Induction of an amnestic inflammatory response by the chemotherapeutic agent in the surviving cells.
2. Induction of mutations by the radiation in the surviving cells that are unable to tolerate the chemotherapy.

Course

It usually subsides within hours to weeks of withdrawal of chemotherapy.

Treatment

Treatment is symptomatic with topical steroids and photoprotection. Discontinuation of the drug will

improve the condition. Systemic corticosteroids may be required in severe cases.[12]

RADIATION ENHANCEMENT

The toxicity of radiotherapy may be enhanced on administration of a chemotherapeutic agent when these two modalities are used concurrently or within 7 days of each other.

Causative Agents

Causative agents doxorubicin, dactinomycin, fluorouracil, bleomycin, hydroxyurea, methotrexate, 6-mercaptopurine.[13]

Clinical Features

The reaction simulates radiation dermatitis and is characterized by erythema, edema, vesiculation with or without ulceration that is localized to the site of radiotherapy. Mucositis may occur. Several factors affect the severity of this phenomenon. These are type and dose of drug, the interval between radiotherapy and chemotherapy, site of radiotherapy, etc. The reaction may be additive or supra additive.

Course

It subsides in days to months.

Treatment

It is symptomatic with local wound care and avoidance of exacerbating factors such as heat, ultraviolet (UV) light and trauma.

INTERACTION WITH UV LIGHT

Phototoxic reactions are caused by dactinomycin, procarbazine, hydroxyurea, methotrexate (Fig. 40.15), mitomycin, thioguanine, fluorouracil, dacarbazine.

Clinical Features

It is characterized by erythema, edema, pain with or without blister formation that may subside with hyperpigmentation. The reaction is seen over sunexposed sites that is face, V area of chest, dorsa of hands and extensor aspect of forearms.

Treatment

Discontinuation of the agent improves the condition. Sun protection with use of protective clothing and broad spectrum sunscreens should be advocated. Physical sunscreens are preferred due to the lower risk of photo allergic reactions. Symptomatic treatment with topical steroids and anti-histamines help in resolution of lesions. Systemic steroids may be used in severe cases.[14]

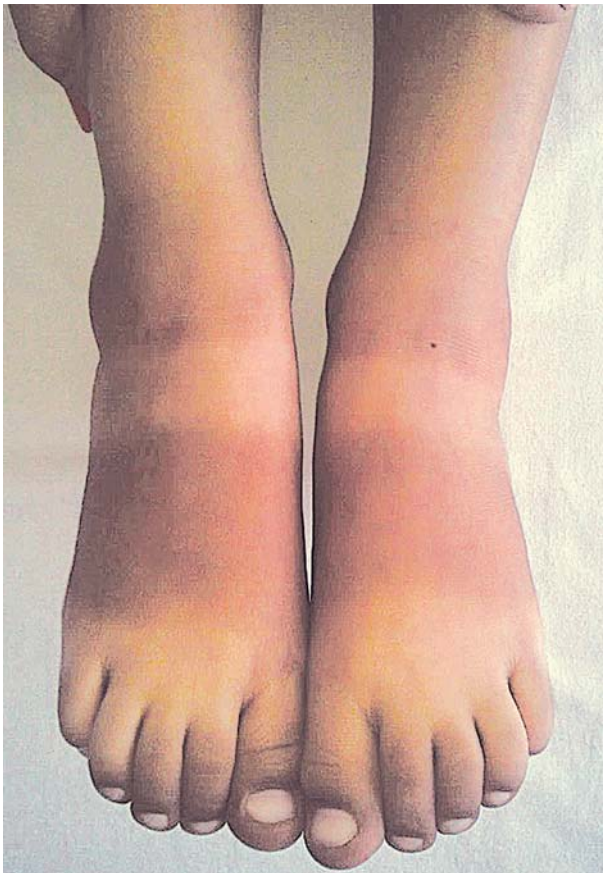

Fig. 40.15: Photosensitivity due to methotrexate in a patient of acute leukemia. (Courtesy of Dr. Grishma Gandhi, Mumbai.)

PHOTO-ONYCHOLYSIS

It has been seen with mercaptopurine, which causes separation of the distal one third of nail from nail bed (Fig. 40.16) and may be associated with tenderness on palpation. Reaction occurs after 2 weeks of exposure to causative drug.[15]

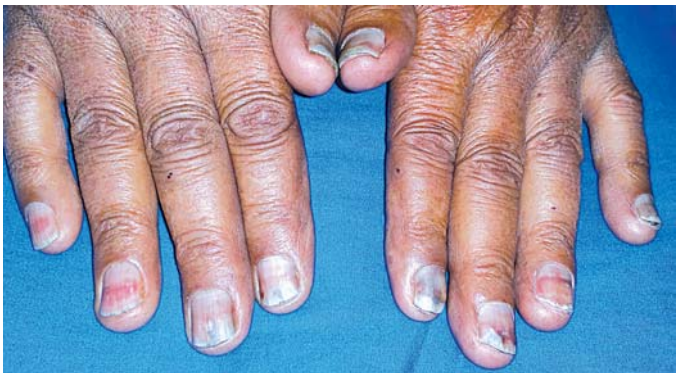

Fig. 40.16: Photo-onycholysis following therapy with 6-mercaptopurine.

UV RECALL REACTION

It is the reactivation of solar erythema classically described with methotrexate therapy. It occurs when the drug is given 1-3 days after UV therapy. It is clinically characterized by erythema, edema, vesiculation and bulla formation in severe cases. The reaction subsides within few weeks even with continuation of methotrexate therapy. It has been described with suramin therapy.

Treatment is symptomatic.

XEROSIS

Xerosis can occur with chemotherapy. It can be mild with fine desquamation or severe with formation of ichthyotic plate-like scales.

Causative Agents

Causative agents include gefitinib and cetuximab.

Pathogenesis

Xerosis may be related to altered differentiation and proliferation of epidermis.

Management

It is treated with emollients.

MORBILLIFORM DRUG ERUPTIONS

Causative Agents

Causative agents include gemcitabine and etoposide.

Clinical Features

Blanching erythematous patches and plaques on trunk that coalesce and may be associated with pruritus.

Course

The rash resolves 1-2 weeks after stoppage of drug.

HYPERSENSITIVITY

Hypersensitivity reactions can occur with any chemotherapeutic agent. However, they are common with a few of them. These can be of type I, II, III, IV. But the most common type is the type 1, IgE-mediated reaction that presents clinically as urticaria, angioedema or rarely as anaphylaxis. Type 1 reaction usually occurs within hours of administration of the drug.[16] The various types of hypersensitivity reactions are summarized in Table 40.4.

Management

Hypersensitivity reactions can be managed with use of antihistamines and corticosteroids. Antihistamines may be used for prophylaxis but steroids are not routinely recommended.[17]

INFLAMMATION OF ACTINIC KERATOSES

Certain chemotherapeutic agents cause inflammation of preexisting actinic keratoses. These are 5-fluorouracil, doxorubicin and sorafenib.[18] These lesions become brightly erythematous, inflamed and may clear. Symptoms are seen 1 week after the start of treatment.

This side effect of 5-FU has been used as a treatment modality for topical therapy of actinic keratosis. The mechanism is unknown but could be due to direct cytotoxic effect as actinic keratoses have rapidly proliferating cells. Role of UV-induced DNA damage

Table 40.4: Types of hypersensitivity reactions

Manifestation	Mechanism	Clinical features/histopathology	Causative agent
Urticaria/angioedema	Type I	Wheals, pruritus, angioedema within 1 hour of administration	L-Asparaginase, bleomycin, carboplatin, docetaxel, epirubicin, etoposide
Erythema multiforme	Type IV	Target or targetoid lesions over acral areas Histopathology: Epidermal necrosis in basal layer and lichenoid infiltrate	Bleomycin, busulfan, chloramphenicol, cyclophosphamide, etoposide, hydroxyurea, methotrexate, paclitaxel
SJS/TEN	Type IV	Erythema multiforme with involvement of mucosal sites (Fig. 40.17), epidermal detachment in TEN	Topical nitrogen mustard, asparaginase, bleomycin, chloramphenicol, cytarabine, doxorubicin, 5-fluorouracil, methotrexate, paclitaxel, procarbazine, suramin

SJS/TEN - Stevens-Johnson syndrome/toxic epidermal necrolysis.

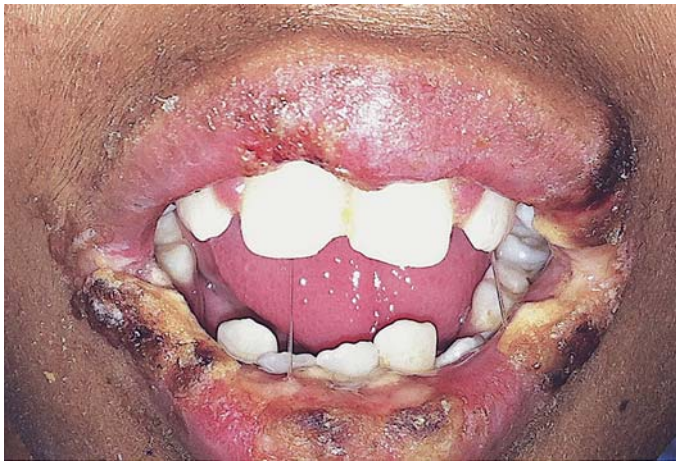

Fig. 40.17: SJS in a patient on bleomycin.

has also been postulated.[19]

Lesions regress 1-4 weeks after stopping the offending drug. Topical steroids can be used for treatment. Further chemotherapy is not contraindicated.

Similar phenomenon has been observed with seborrheic keratosis.

Flare up of squamous cell carcinoma has been seen with fludarabine.[20]

UNIQUE DRUG SPECIFIC REACTIONS

These have been depicted in Table 40.5.

Table 40.5: Unique drug specific reactions

	Drug	Adverse effect
1	EGFR inhibitors	Curly hair, trichomegaly[21]
2	Estramustine	Estrogen-related adverse effects[22]
3	Fludarabine	Paraneoplastic pemphigus[23]
4	Gemcitabine	Peripheral edema[24]
5	Hydroxyurea	LP-like eruption, dermopathy (lichenoid papular eruption on hands and feet)[25]
6	Taxanes	Fluid retention syndrome[26]
7	Anthracyclines	Erythematous macules, papules and plaques with histological changes of interface dermatitis

EGFR - epidermal growth factor receptor; LP - lichen planus.

LEARNING ESSENTIALS

- Chemotherapeutic agents may be associated with a variety of cutaneous adverse effects that may be benign or life-threatening.
- Common side effects include alopecia, hyperpigmentation, mucositis, and nail dystrophies.
- Extravasation, radiation recall and enhancement, AE, NEH, syringosquamous metaplasia and autoimmune phenomenon are the rare adverse effects.
- It is important for the treating physician to recognize these drug reactions, differentiate them from other cutaneous disorders in cancer patients so as to plan appropriate management.

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Chapter

41

Cutaneous Adverse Drug Reactions to Targeted Therapies

Abhay Mani Martin • Deepthi N.S.

SUMMARY

Cancer chemotherapy has witnessed a shift from "traditional" cytotoxic chemotherapeutics to "newer" targeted therapy. Targeted therapies use therapeutic agents that are directed specifically toward the molecular pathways involved in the pathogenesis of cancer. They are considered to be specific for diseased cell populations while sparing normal cells. This class of drugs has changed the management protocols for most cancers. An increasing array of drugs of this class is being introduced into the market. Skin being a prominent target in the molecular pathway of rapidly multiplying cells, the dermatologist is called upon to diagnose adverse reactions, which may arise as an offshoot of therapy. This chapter deals with cutaneous adverse drug reactions that practitioners are likely to encounter with targeted molecular therapies.

INTRODUCTION

Since the approval of imatinib, a BCR-ABL tyrosine kinase inhibitor, for chronic myelogenous leukemia in May 2001,[1] cancer chemotherapy has witnessed a paradigm shift from traditional chemotherapeutics to newer targeted therapy directed specifically against the various molecular pathways involved in the pathogenesis of cancer. While these agents have a lower rate of systemic toxicity owing to their specificity, a whole range of class-specific cutaneous toxicities have emerged.[2,3] Knowledge of the cutaneous adverse reactions to these drugs is essential to recognize the adverse drug reactions (ADRs), to decide on dose reduction or drug discontinuation and to take appropriate management decisions, thereby resulting in improved quality of life.

To ensure uniformity and comparability across studies, the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) has been used widely for grading of the ADRs due to anticancer drugs.[4] Chen, et al. have reviewed the dermatological aspects of the NCI-CTCAE version 4 published in May 2009 (Box 41.1).[5]

The molecular targets of targeted therapy on the cell are unique and it is necessary to understand their mechanisms of action to study the effectiveness of these drugs. They are summarized in the diagram (Fig. 41.1).

Box 41.1: Classification of targeted anticancer therapies

- Epidermal growth factor receptor (EGFR) inhibitors
- Multikinase inhibitors (MKIs)
- BRAF inhibitors
- Proteasome inhibitors
- Antiangiogenic agents
- Pi3K-AKT-mTOR pathway inhibitors
- Hedgehog signaling pathway inhibitors

EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITORS

EGFR is a 170-kD transmembrane glycoprotein with an extracellular ligand-binding domain and an intracellular tyrosine kinase protein. When the ligand binds to the extracellular domain, autophosphorylation of the tyrosine kinase leads to activation of a signal transduction pathway, which regulates cell proliferation and differentiation.[6] Over expression of EGFR has been found to be associated with development and progression of many cancers. Moreover, specific mutations in the EGFR protein are present in a subset of patients.[6,7] EGFR inhibitors

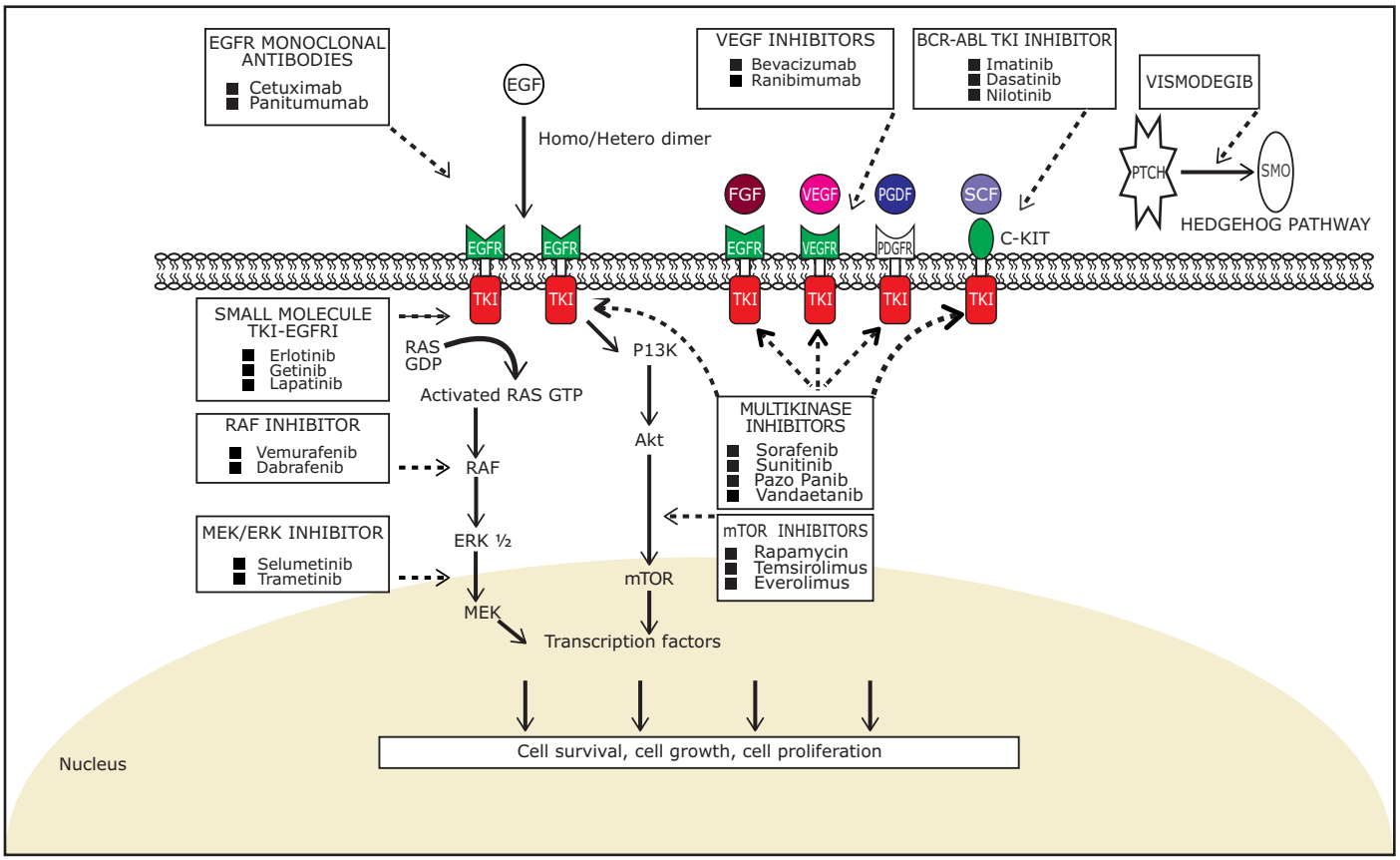

Fig. 41.1: A representative schematic diagram of molecular targets of targeted therapy with site and mechanism of action of different agents.

were among the earliest group of targeted anticancer agents and are broadly classified as follows:

1. Monoclonal antibodies to EGFR—e.g. cetuximab, panitumumab
2. Small molecule tyrosine kinase inhibitors—e.g. erlotinib, gefitinib, lapatinib

They are used in various cancers including colorectal cancers, squamous cell carcinomas of head and neck and in non–small cell lung carcinoma (NSCLC).[8]

EGFR is expressed widely in the skin, maximally in the stratum basale of the epidermis. It is also expressed in the dermal papilla, pilosebaceous unit, outer root sheath of the hair follicle and dermal capillaries.[8,9]

As a consequence, EGFR inhibitors have an effect on the survival, proliferation, and differentiation of skin and adnexal structures and hence a wide range of cutaneous adverse drug reactions (CADRs) are encountered with this group of drugs.[8]

The adverse effects of EGFRs are proposed to be due to the impairment of epidermal differentiation and barrier function, and increased inflammation due to expression of chemokines like CCL18, CXCL1, CXCL9, and XCL1.[8] The incidence of CADRs with EGFR inhibitors has been reported to be between 50% and 90%,[2] with severe skin toxicity in 20%–35% cases.[8]

Lacouture and Lai in 2006 proposed the acronym PRIDE syndrome (Papulopustules and/or paronychia, Regulatory abnormalities of hair growth, Itching and Dryness due to EGFR inhibitors) to describe the dermatological adverse effects of EGFR inhibitors.[10,11]

The CADRs to EGFR inhibitors are listed in Table 41.1.

Acneiform / Papulopustular Rash

This is the most common CADR associated with EGFR inhibitors (>75%)[3] and it has been variously described as papulopustular rash, acneiform rash, maculopapular rash and monomorphic pustular rash in different reports.[9] It typically starts within the first 2 weeks of starting treatment. Follicular erythematous papules and pustules start in the seborrheic areas of head and trunk (Fig. 41.2A and B) and gradually become generalized (Fig. 41.2C), sparing palms and soles. Unlike acne, comedones are

Table 41.1: CADRs to epidermal growth factor inhibitors (erlotinib, gefitinib, lapatinib, cetuximab, panitumumab)

1. Papulopustular rash/acneiform eruption—most common[3,9]
2. Xerosis (35%)[2,8]
3. Nail changes (17.2%)[3,8]
   a. Paronychia
   b. Onycholysis
   c. Pyogenic granuloma-like lesions
   d. Dyspigmentation and brittle nails
4. Hair changes[3,8,12]
   a. Scalp hair—Slow growth, fine brittle and kinky
   b. Eyelash—Trichomegaly and trichorrhexis
   c. Eyebrows—Hypertrichosis
   d. Hirsutism in females
   e. Alopecia with/without scalp inflammation
5. Telangiectasia[2]
6. Photosensitivity and hyperpigmentation of exposed areas of skin[8,13]
7. Mucositis[3,14]
   a. Oral aphthae, xerostomia, geographic tongue
   b. Nasal ulcers
   c. Vaginal dryness, vulvovaginitis, balanitis
   d. Conjunctivitis and keratitis
8. Increased severity of radiation dermatitis[2,7]
9. Pruritus[3]
10. Other skin lesions[3,9]
    a. Transient acantholytic dermatosis
    b. Necrolytic migratory erythema-like skin lesion (gefitinib)
    c. Sycosis (gefitinib)
    d. Pyoderma gangrenosum like lesions (gefitinib)
    e. Purpuric drug eruption
11. Hand–foot syndrome (HFS)/acral erythema[9]
12. Hyposalivation and taste abnormalities[8]

characteristically absent and the rash is pruritic.[2,9] It evolves in a dose-dependent manner and clears completely in a few weeks of stopping treatment. Histology shows predominantly neutrophilic folliculitis and perifolliculitis with hyperkeratosis and ectatic infundibula.[3,9] The monoclonal antibodies are more commonly associated with severe rash than the small molecule TKI inhibitors.[7]

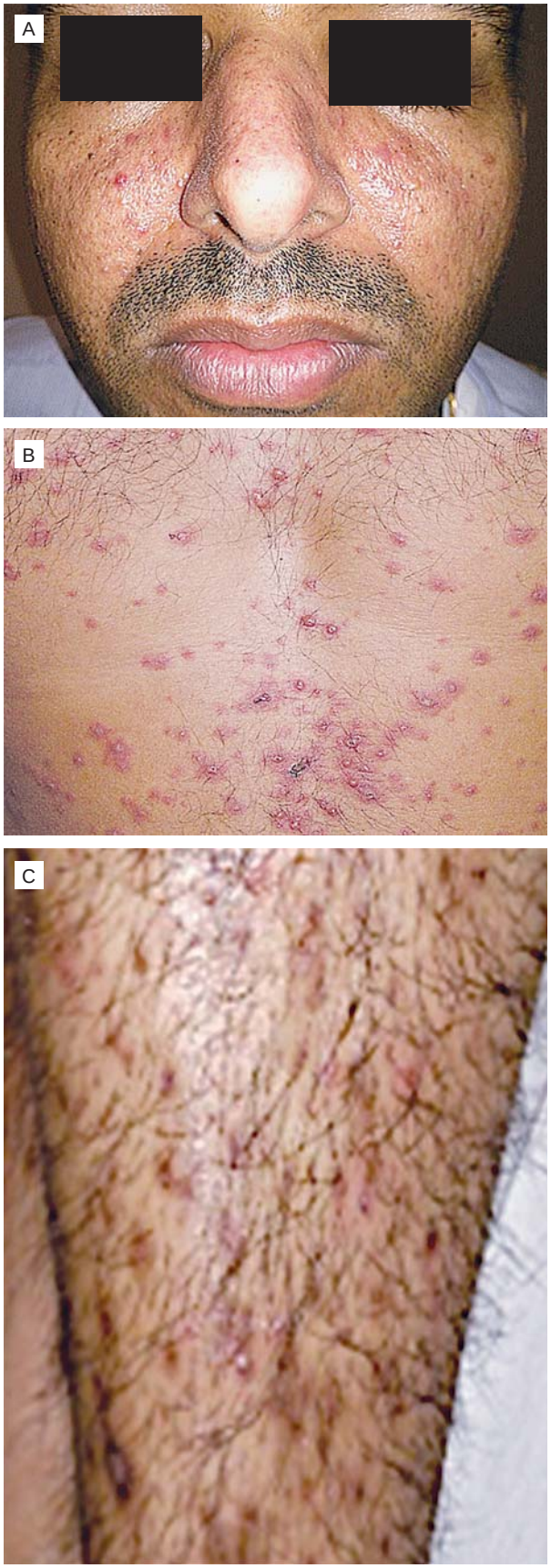

Fig. 41.2: Erythematous papulopustular lesions over (A) face; (B) chest and abdomen induced by EGFR inhibitors. Comedones are characteristically absent. Follicular distribution of lesions over legs (C).

The severity grading of the EGFR inhibitors-induced acneiform rash is given in Table 41.2. The Multinational Association of Supportive Care in Cancer (MASCC) Skin Toxicity Study Group has proposed an alternative grading of EGFR-induced skin toxicities with inclusion of relevant dermatologic nomenclature and also recommended the term "papulopustular rash" over "acneiform rash" to emphasize its clinical and histological differences from acne.[15]

The occurrence and severity of the papulopustular rash has shown a positive correlation with treatment response in colorectal cancers and NSCLC[8] and its role as a surrogate marker of treatment response is under evaluation.[9,16]

Emollients and topical corticosteroids may be useful in mild cases but in severe cases their adverse effects outweigh any potential benefit. The role of retinoids is controversial and the long latent period of oral retinoids limits its use in acute toxicity.[9] Oral and topical antibiotics used include doxycycline, minocycline, clindamycin, erythromycin and metronidazole. Of these, the tetracycline derivatives have shown the most benefit. Although doxycycline has a better safety profile in patients with concomitant renal impairment, minocycline has lesser photosensitivity.[7] Although there is a theoretical risk that tetracycline-induced inhibition of lymphocyte proliferation and neutrophil migration might interfere with the therapeutic effect of EGFR inhibitors, this has not been demonstrated clinically.[8] Prophylactic use of minocycline and doxycycline with EGFR inhibitors has been shown to reduce the incidence and severity of skin toxicity by Scope et al. and in the skin toxicity evaluation protocol with panitumumab (STEPP) study by Lacouture et al.[8,17,18]

Xerosis

Xerosis of skin with scaling (Fig. 41.3), occasionally associated with painful fissuring of palms and soles, is the second most common CADR seen with EGFR inhibitors (35%).[2,8] It is most prominent in the first to third month of therapy. The disruption of skin barrier can lead to secondary bacterial or viral infections.[3] Patients are advised to avoid mechanical trauma, use of harsh soaps, frequent washing and use of hot water while starting the treatment. Frequent use of emollients with antihistamines to control the pruritus is recommended. Topical corticosteroids when used should preferably be in ointment form.[3,8]

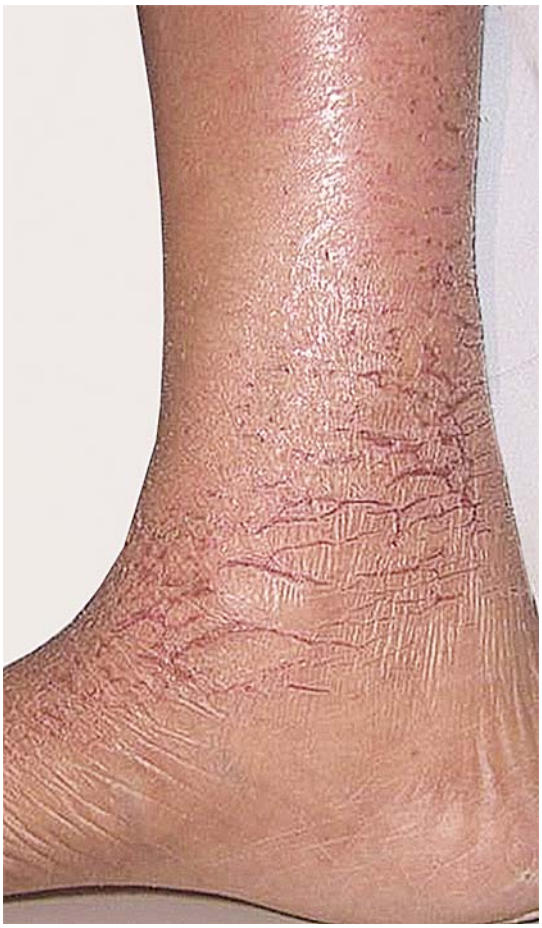

Fig. 41.3: Xerosis of skin is seen with EGFR inhibitors, multikinase inhibitors, MEK/ERK inhibitors, m-TOR pathway inhibitors. This patient was on gefitinib for small cell lung carcinoma.

Table 41.2: NCI-CTCAE grading of EGFR inhibitors-induced acneiform rash

Grade 1	Papules and/or pustules covering <10% body surface area (BSA), which may or may not be associated with symptoms of pruritus or tenderness.
Grade 2	Papules and/or pustules covering 10%–30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental activities of daily living (ADL).
Grade 3	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated.
Grade 4	Papules and/or pustules covering any percent of BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences.
Grade 5	Death.

Mucosal Changes

Oral mucosal involvement is seen in 5%–23% patients treated with monoclonal antibodies to EGFR and presents as mucositis, xerostomia, oral aphthae, geographic tongue, dysphagia and pharyngitis.[3,14] Mucositis caused by EGFR inhibitors is seen as a diffuse erythema of the mucosa unlike the classical ulcerative lesions seen with cytotoxic agents.[14]

Ocular adverse effects are seen in 12%–14% of cases in the form of conjunctivitis, keratoconjunctivitis sicca and trichomegaly leading to blurring of vision and ocular discomfort.[3]

Paronychia

Paronychia with severe tenderness is seen in 10%–20% patients and arises 4–8 weeks after starting treatment. It can be associated with slowing of nail growth, onycholysis, onychodystrophy, onychoschizia and pyogenic granuloma-like inflammation (Fig. 41.4).[8,10] It is more common in the fingers than the toes and takes a long time to resolve after cessation of treatment. Topical antibiotics and emollients are beneficial. Doxycycline, probably by its anti-inflammatory effect, has also been found to be effective in treating paronychia.[13] Involvement of the nail bed leads to onycholysis while that of the nail matrix leads to dyspigmentation and brittleness of nails.[3]

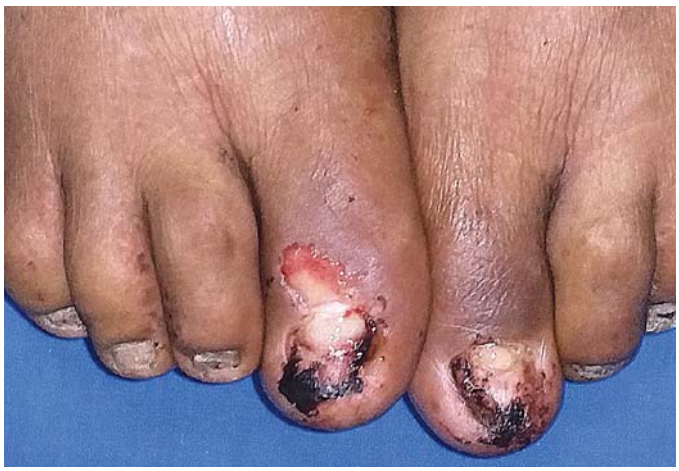

Fig. 41.4: Targeted therapy agents can cause periungual and ungual changes. The above case was on gefitinib therapy.

Hair Changes

Hair changes are seen from the second or third month of treatment. While the scalp hair becomes finer, more brittle, and grows at a slower rate, the eyelashes and eyebrows show trichomegaly (longer and thicker), curling and trichorrhexis, which may result in keratitis.[8] Rodriguez and Ascaso have reported the occurrence of poliosis in addition to trichomegaly during cetuximab therapy.[12] Eyelash clipping every 2–4 weeks is advised.[7] Hirsutism may be seen.[3]

Both cicatricial and noncicatricial alopecia have been reported with EGFR inhibitors. It begins as a frontal or patchy hair loss 2–3 months after starting treatment that may progress to a diffuse alopecia with continued treatment. Nonscarring alopecia resolves spontaneously after treatment discontinuation although the quality and texture of hair may be altered. Minoxidil has been found to be beneficial but it can precipitate or worsen scalp pruritus. Cicatricial alopecia occurs secondary to inflammatory lesions on scalp, face or trunk. Early use of topical corticosteroids in such lesions is advised to prevent the same.[7] Chen et al. have found oral doxycycline to be beneficial in a topical and intralesional steroid resistant case of scarring alopecia.[19]

Photosensitivity

EGFR inhibitors, particularly gefitinib (10%), also produce photosensitivity leading to telangiectasia and hyperpigmentation, particularly over exposed areas. Histology shows increased melanin in basal keratinocytes and superficial dermal macrophages.[13] The importance of strict photoprotection must be emphasized to the patients right from the beginning. Hyperpigmentation gradually fades over months.[8]

Miscellaneous

EGFR inhibitors have been reported to increase the severity of radiation dermatitis in patients undergoing concomitant radiotherapy in several studies. Severe cases may develop skin necrosis and full thickness ulceration of skin. Potent topical corticosteroids have been found to be beneficial in addition to emollients, antihistamines and antibiotics to treat secondary infection.[2,7]

Eilers et al. found a higher prevalence of cutaneous infections, particularly bacterial, in patients who developed CADRs to EGFR inhibitors.[20]

MULTIKINASE INHIBITORS

This group includes drugs that inhibit multiple tyrosine kinase receptors: Sorafenib inhibits RAF kinase, vascular endothelial growth factor receptor (VEGFR) 2 and 3, platelet-derived growth factor receptors beta (PDGFR-β), FMS-like tyrosine kinase 3 (Flt-3), c-Kit protein, and RET receptor tyrosine kinase, whereas sunitinib inhibits VEGFRs 1–3, PDGFR-α, c-Kit, Flt-3, colony-stimulating factor receptor 1, and the glial cell line–derived neurotrophic factor receptor.[3,21] They have been used in renal cell carcinoma, hepatocellular carcinoma, and

gastrointestinal stromal tumors with good results.[22] The incidence of CADRs with sorafenib and sunitinib has been reported to be 74%–91% with the commonest being HFS.[2] Table 41.3 lists some of the CADRs to multikinase inhibitors (MKIs).

Table 41.3: CADRs to MKIs (sorafenib, sunitinib, pazopanib, and vandetanib)

1. HFS/palmoplantar erythrodysesthesia[2]
2. Facial erythema and seborrheic dermatitis–like rash[2,9]
3. Transient yellow discoloration of skin (sunitinib)[9]
4. Subungual splinter hemorrhages[2]
5. Hair changes[2,3]
   a. Alopecia
   b. Reversible hair depigmentation
6. Xerosis[3]
7. Eruptive benign naevi[3]
8. Pruritus[3]
9. Inflammatory eruptions[3]
   a. Disseminated morbilliform rash
   b. Toxic epidermal necrolysis (TEN)
   c. Drug hypersensitivity syndrome (DHS)
   d. Papulopustular rash (~3%)
10. Stomatitis and cheilitis[14,21]
11. Pyoderma gangrenosum like ulcerations (sunitinib)[3]
12. Hyperkeratotic squamoproliferative lesion (sorafenib)[3]
13. Blue grey macules of dyspigmentation (vandetanib)[3]
14. Scrotal skin desquamation (noted with pazopanib)

Hand–Foot Syndrome

Also known as hyperkeratotic hand foot skin reaction (Table 41.4) or palmoplantar erythrodysesthesia, HFS occurs in the 20%–78% of patients in the first 2–4 weeks of treatment with maximum incidence with sorafenib (10%–63%), followed by sunitinib (10%–28%) and pazopanib (11%).[2,9] It has also been noted with the recently introduced drug Regorafenib. Hyperkeratotic tender plaques with a peripheral halo of erythema are seen on palms (Fig. 41.5A) and soles (Fig. 41.5B), predominantly over pressure sites such as tips of fingers and toes, heels and metatarsophalangeal area of sole. Areas of friction like skin overlying metacarpophalangeal or interphalangeal joints, dorsum of hands, elbows and knees may also be involved (Figs. 41.5C and D).[22,23] Lateral sides of fingers and periungual zones may be affected and some cases may develop edematous lesions, desquamation, and fissures leading to significant discomfort, impairing the range of movement and weight bearing. Patients describe an intolerance to contact with hot objects, pain, and a burning sensation causing difficulty in walking. In severe cases, large tense blisters may develop.[3,22,23] In darker skin races (Fitzpatrick skin types 4 and 5) the syndrome presents as hyperpigmentation of the palms and soles (Figs. 41.6A-D) as erythema is not well appreciated. Those of Dravidian descent in South India with darker skin types are typical examples in India (author's view).

Histology shows hyperkeratosis with focal parakeratosis and nonspecific dermal infiltration with dilated blood vessels. Keratinocyte damage in the form of vacuolar degeneration and keratinocyte necrosis leading to intraepidermal cleavage is seen. Intracytoplasmic eosinophilic inclusion bodies are specific for sorafenib-induced HFS.[24,25]

Table 41.4: HFS: grading, features, treatment and preventive measures

Grade	Features	Treatment	Prevention
Grade 1	Minimal skin changes/ dermatitis, no pain	Emollients, topical keratolytics and cold water soaks.	• Use of moisturizers after bath. • Use of Gloves and socks overnight with moisturizer on skin. • Padded soles for footwear.
Grade 2	Skin changes (e.g. blisters, peeling, bleeding, edema) or pain; no impairment of patient's daily activities	Potent topical corticosteroids with or without occlusion may be required in addition to above measures.	• *For blisters*: Luke warm or salt water soaks and padded footwear. • *For dry/peeled or fissured skin*: Frequent use of moisturizers if dry/peeled skin. • *For edema*: Foot end elevation.
Grade 3	Ulcerative dermatitis or skin changes with pain; patient's daily activities impaired	Dose reduction by 50% or interruption of treatment may be needed.	• Luke warm water soaks. • Topical antibiotic use on wounds. • Analgesic use if severe pain.

Modified from NCI-CTCAE grading of HFS and treatment[2,3], and Management and Preventive measures in hand–foot skin reaction.[22,23]

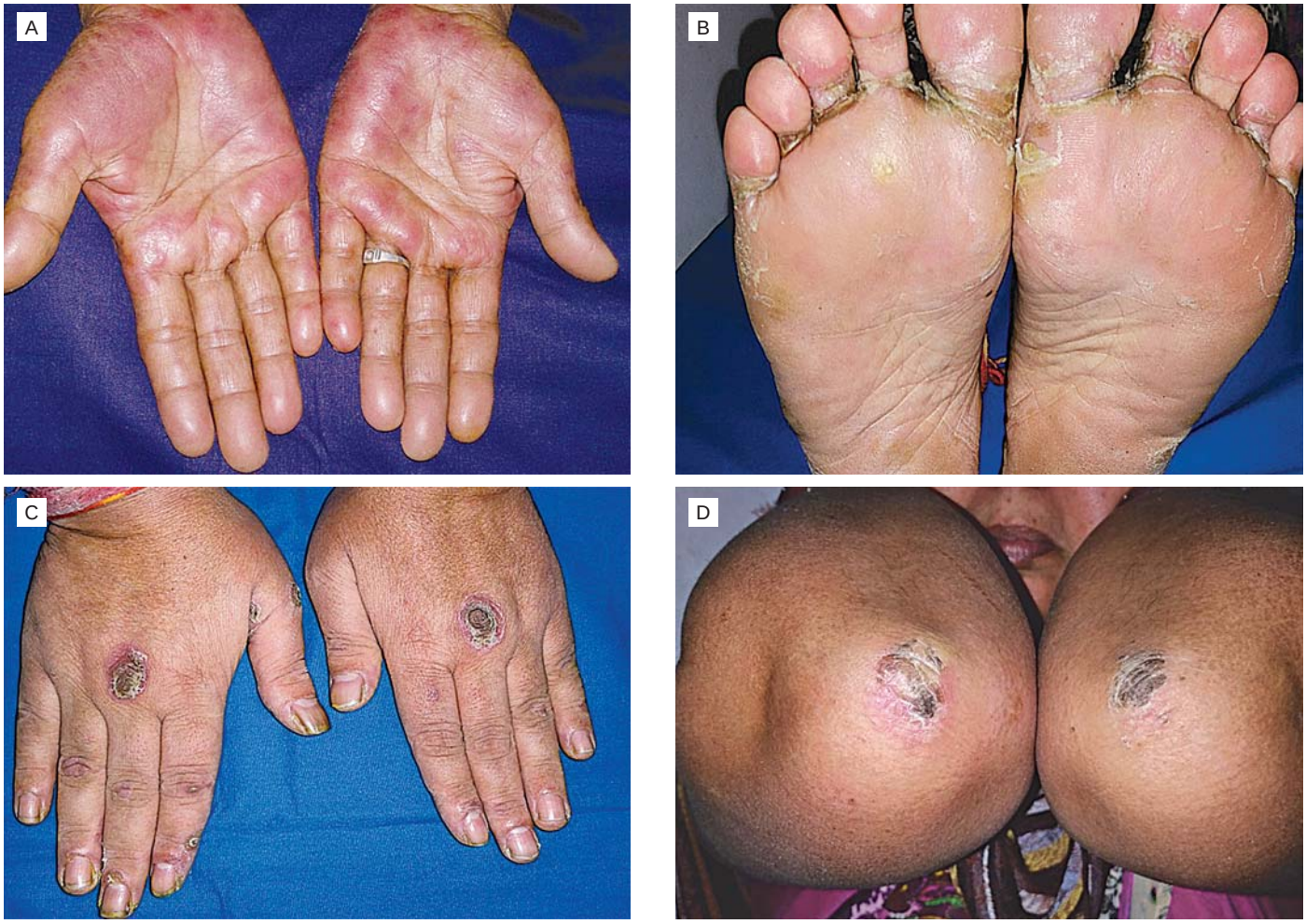

Fig. 41.5: Sorafenib induced hand and foot syndrome. (A) Erythematous plaques over palms involving the pressure bearing area with sparing of central, non-pressure bearing region; (B) Hyperkeratotic plaques with erythematous halo, exfoliation and fissuring over tips of toes, metatarsophalangeal area, heel and lateral sides of sole; (C) Psoriasiform plaque over dorsum of hands, also note the involvement of interphalangeal joints and tips of fingers and (D) hyperkeratotic psoriasiform plaques surrounded by erythematous halo over elbows.

The mechanism of MKI-induced HFS is unclear. There is no evidence of secretion of the drug into the eccrine glands. It is suggested that the combined inhibition of VEGFR and PDGFR results in vessel regression and reduced vessel repair capacities.[3,22,25] Recently, Zimmerman et al. identified organic anion transporter 6 (OAT6) as a transporter regulating the uptake of sorafenib in keratinocytes, which resulted in cytotoxicity in vitro by a TAK1-dependent mechanism. Hence these effects could be reversed by cotreatment with OAT 6 inhibitor probenecid.[26]

Sorafenib-induced HFS is less severe in comparison to classical HFS caused by cytostatic agents, and is characterized by localized hyperkeratosis with surrounding erythema in contrast to the diffuse symmetrical involvement seen with the latter. [22] The clinical features of different grades of HFS are summarized in table 41.4.

Seborrheic Dermatitis–like Rash

A seborrheic dermatitis–like rash occurs 1–2 weeks after starting treatment, with erythema and scaling over face and scalp, which may be preceded by scalp dysesthesia.[2,9] The facial erythema mainly affects the mediofacial area with periorbital sparing and is aggravated by hot temperatures.[27] Histology shows compact hyperkeratosis with loss of basket weave configuration of stratum corneum.[2] Topical emollients, 2% ketoconazole, and topical steroids have been found to be beneficial and the condition resolves spontaneously within 8 weeks of stopping treatment.[9]

A transient yellow discoloration of skin is seen after 1 week of sunitinib therapy at doses of >50 mg/day and is associated with yellow coloration of the urine, probably due to direct excretion of drug and its metabolites. The exact cause of this phenomenon

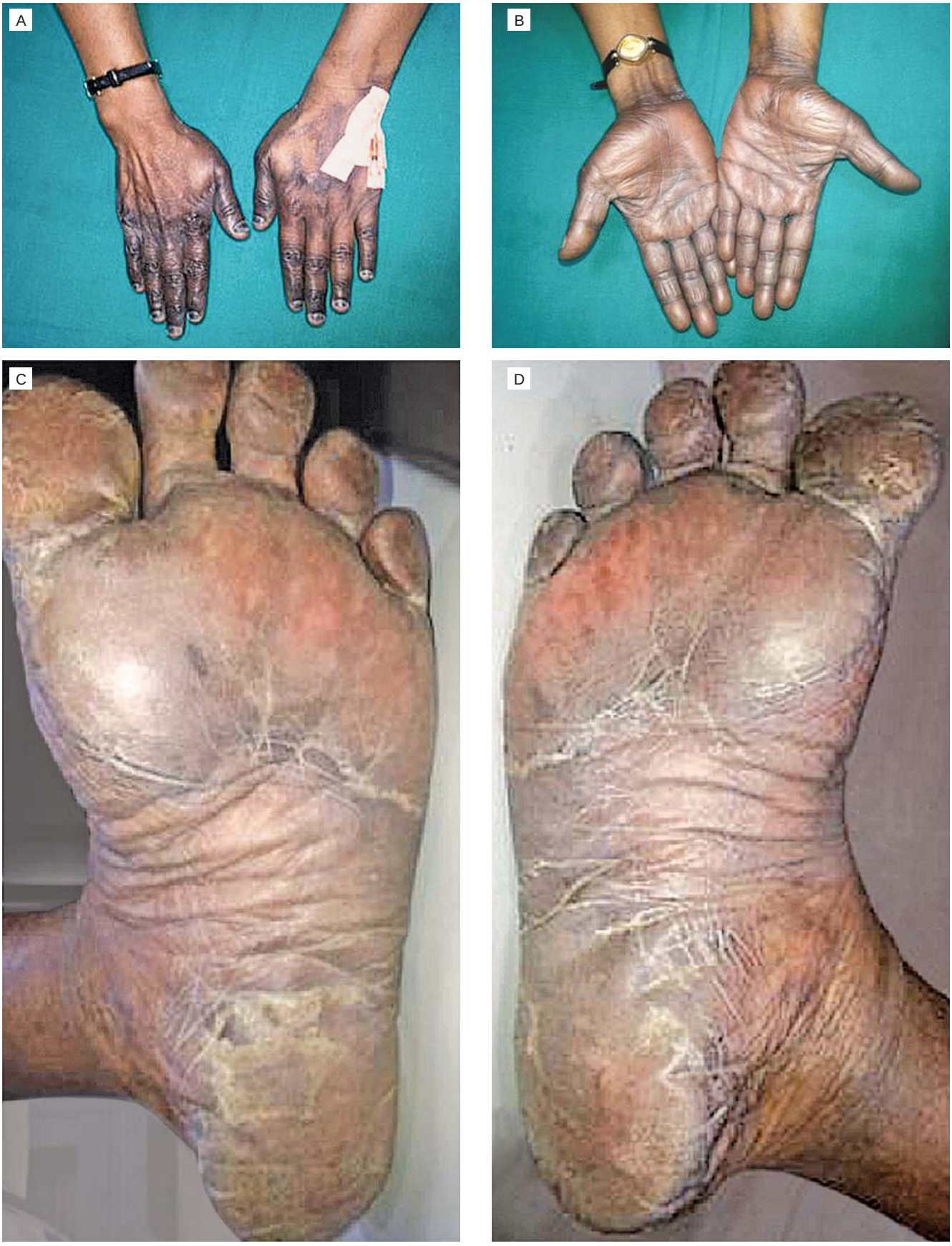

Fig. 41.6: Hyperpigmentation on dorsal (A) and palmar (B) aspect of hands and soles (C & D), due to sorafenib. Hyperpigmentation rather than erythema is a prominent presentation in dark skinned races (4 and 5 Fitzpatrick skin types), as is seen in South India.

is not known.[9,21] *Facial cystic lesions* including Fitzpatrick lesions, milia and epidermal cysts have also been reported in a small number of patients treated with sorafenib.[21,27]

Painless subungual splinter hemorrhages are seen in 60%–70% of patients during the first 1–2 weeks of therapy and resolve spontaneously. These are almost exclusively seen on fingernails in a distal distribution.[2,27] The inhibition of VEGFR prevents normal repair of delicate spiral capillaries in the nail bed after trauma, resulting in spontaneous hemorrhages.[9]

Hair Changes

Thinning of hair and patchy alopecia is seen most commonly with sorafenib (44%), followed by sunitinib (5%–21%) and pazopanib (8%–10%).[3] Slowing of beard growth is seen in men.[2] Typically, this side effect is noted with sorafenib, but not with imatinib or sunitinib.[28] Reversible depigmentation of hair is seen in 60%–64% of patients on sunitinib, which begins 5–6 weeks after starting treatment and resolves 2–3 weeks after treatment cessation. Occasionally, bands of normal and depigmented hair are seen corresponding to the period of treatment.[9] Scalp biopsies revealed no melanocyte destruction in such cases.[2] No hair shaft abnormalities are noted.

Xerosis Cutis

This is less frequent and is noted on the inferior limbs and occurs in 10%–20% of patients.[3]

Oral Lesions

Stomatitis and cheilitis were reported in 26%–36% patients usually occurring in the first 1–8 weeks of starting treatment.[21] Other oral adverse effects include dysgeusia, voice changes, tongue/throat pain, dry mouth and gum bleeding.[14]

Vasculitis like Skin Lesions

A 65 year old gentleman with Gastrointestinal Stromal Tumour (GIST) with a lichenoid eruption like clinical picture (Fig. 41.7A), spongiotic reaction in the epidermis and prominent vasculitic changes in the dermis including fibrinoid necrosis and RBC extravasation, was noted (unpublished anecdotal report encountered by author-AMM). Another child on imatinib for chronic myelogenous leukemia was seen to develop palpable purpuric lesions (Fig. 41.7B), characteristic of leukocytoclastic vasculitis.

Scrotal Skin Desquamation

A unique side effect of pazopanib is scrotal skin desquamation causing a burning sensation and erythema of the scrotal skin.[33] The symptoms subside on drug withdrawal. The exact mechanism is not known. One such case of scrotal desquamation (Fig. 41.8A), was encountered by one of the authors -AMM (unpublished). The same patient also developed hand foot syndrome (Figs. 41.8B) and greying of hair on the eyebrows and eyelashes (Fig 41.8C).

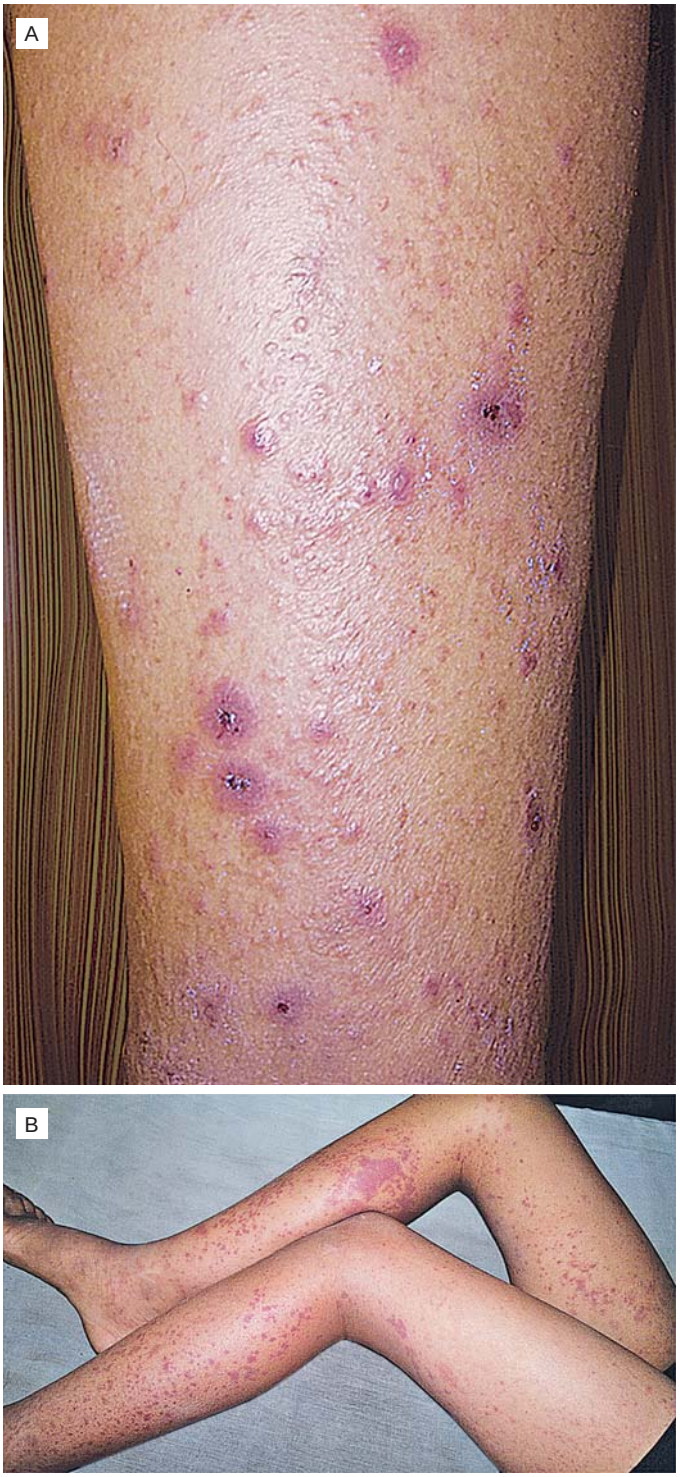

Fig. 41.7: (A) Imatinib induced cutaneous vasculitis in an elderly, on treatment with Imatinib for Gastrointestinal Stromal Tumour (GIST); (B) Cutaneous vasculitic lesions in a child receiving imatinib for leukemia.

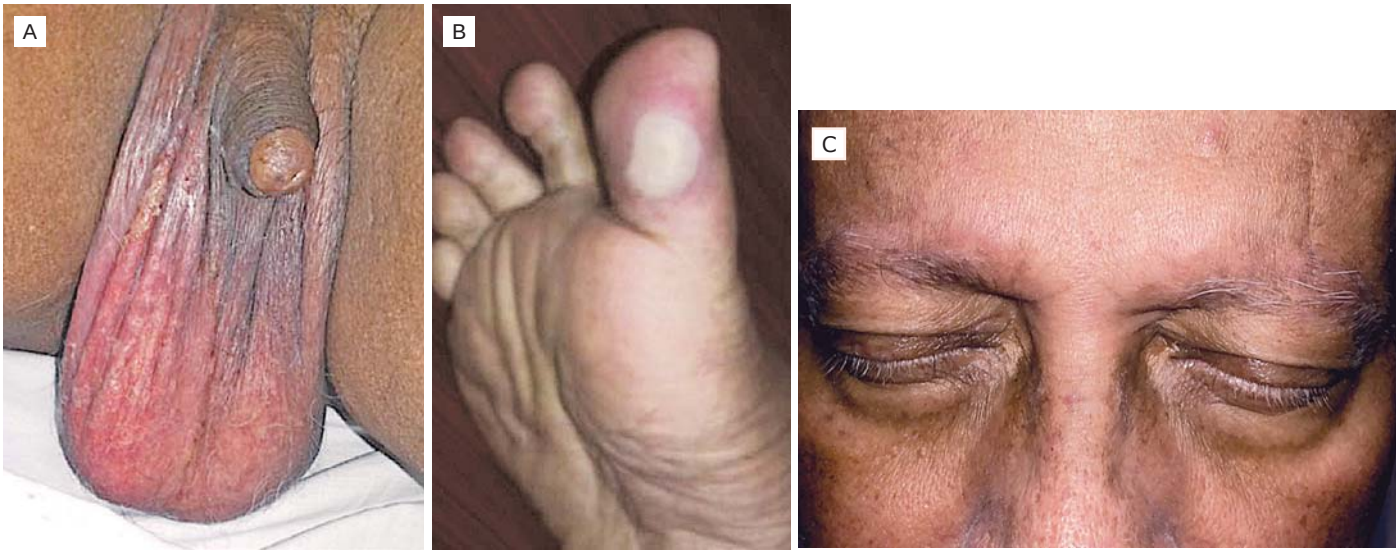

Fig. 41.8: Pazopanib induced cutaneous ADRs. A patient on pazopanib developed the following rashes at different points in time: (A) Scrotal skin desquamation with tenderness; (B) Focal tender hyperkeratotic areas on the feet; (C) Greying of eyebrows and eyelashes.

Miscellaneous

Vandetanib, an MKI targeting EGFR, VEGFR1–3, and RET, has been reported to produce varying grades of photosensitization (37%) and hyperpigmentation (19%) of the skin by Giacchero et al.[29]

Sorafenib, but not sunitinib, has been reported to cause multiple rapidly progressing keratoacanthomas and squamous cell carcinomas, which often regress quickly after interruption of treatment. Most lesions can be managed with cryotherapy or excision but rarely termination of treatment may be needed.[30–32]

BRAF INHIBITORS

BRAF is an upstream activator of the mitogen-activated protein kinase (MAPK) pathway.[33] A high frequency of activating mutations of the RAS/RAF/MEK/ERK pathway is present in various subsets of melanoma, of which BRAF mutations are the commonest. In addition to 40%–70% of melanomas, BRAF mutations are also seen in hairy cell leukemia, papillary carcinoma thyroid, ovarian, colorectal, and prostate tumors. Vemurafenib and dabrafenib have shown significant success in the treatment of these cancers.[33,34] Table 41.5 enumerates a few CADRs to BRAF inhibitors.

Keratinocytic proliferations are a characteristic CADR associated with BRAF inhibitors seen in 50%–86% of patients. It ranges from benign (cutaneous papillomas, keratoacanthomas) to premalignant (actinic keratosis) and malignant (mostly well differentiated squamous cell carcinomas).[34] Inhibition of RAF in the presence of wild-type BRAF cells has

Table 41.5: CADRs to BRAF inhibitors (vemurafenib, dabrafenib)

1. Keratinocytic neoplasia/proliferations[33,34]
   a. Verrucal keratosis (50%–86%)
   b. Keratoacanthoma (20%–30%)
   c. Squamous cell carcinoma (SCC)
2. Morbilliform skin rash[33,34]
3. Photosensitivity—UV-A sensitivity[34]
4. Pruritus[33]
5. Palmoplantar dysesthesia—hyperkeratotic hand foot reaction (up to 60%)
6. Keratosis pilaris like reaction (33%)[33,34]
7. Seborrheic dermatitis–like eruption
8. Melanocytic lesions[33–35]
   a. Changes in preexisting nevi and eruptive nevi
   b. Primary melanoma
9. Painful lobular panniculitis[36]
10. Other less common ADRs[33–35]
    a. Nonscarring alopecia
    b. Facial erythema
    c. Acantholytic dermatoses
    d. Gingival, nipple and vulvar hyperkeratosis
    e. Hidradenitis suppurativa
    f. Eruptive milia, epidermoid cysts
    g. Radiosensitization and an induction of radiation recall dermatitis
    h. Sarcoid-type granulomatous eruption

been shown to cause paradoxical activation of MAPK pathway through dimerization of RAF isomers. This leads to unmasking of oncogenic events in keratinocytes with preexisting sun-induced RAS mutation and proliferation of keratinocytes. In fact, combination of RAF inhibitors with MEK inhibitors reduces the incidence of keratinocyte proliferations by downstream inhibition of MAPK pathway.[33]

The term "verrucal keratosis" is used to describe the keratotic lesions caused by BRAF inhibitors, seen clinically as white hyperkeratotic papules over both sun-exposed and covered areas and histologically characterized by hyperkeratosis, acanthosis, papillomatosis, with low-to-moderate levels of epidermal dysplasia and absence of viral verrucal verrucal changes or keratohyalin granules.[33,37]

Keratoacanthomas occur in 20%–30% cases and invasive SCCs are much rarer. Most of these occur in the first 6 months of treatment, with the median time to presentation being 8 weeks.[33] It is almost always accompanied by actinic skin changes. These keratinocytic proliferations generally regress after treatment cessation and careful monitoring to watch for malignant transformation is advisable. Benign papillomas can be managed by cryotherapy, whereas suspicious lesions (erythematous, infiltrated, and painful) may be excised and histological examination performed.[34]

A morbilliform eruption with folliculocentric smooth papules on the trunk and extensor aspects of extremities is seen in 36%–68% patients on vemurafenib. Some lesions resemble an exaggerated form of keratosis pilaris with background erythema. Histologically, there is perifollicular lymphocytic infiltration with perivascular mixed infiltration.[33,34] Darier's-like or Grover's-like acantholytic dyskeratosis has been reported in a clinicopathologic study by Chu et al.[38] The rash may be associated with fever, arthralgia and acute kidney injury. Mild-to-moderate cases may be managed with emollients, topical steroids and antihistamines, whereas severe cases require systemic corticosteroids and treatment interruption.

Photosensitivity is seen early in the treatment with vemurafenib but not with dabrafenib. The minimal erythema dose (MED) for UV-A (but not UV-B) is significantly reduced and even brief exposure can lead to painful erythema with severe cases developing blistering and burns. Patients are advised strict sun protection with potent UV-A blockers such as titanium dioxide, zinc oxide, and avobenzone along with sun avoidance and protective clothing.[34]

Painful lobular panniculitis involving both upper and lower limbs with arthralgia is seen with BRAF inhibitors. While most patients have intermittent painful nodules that can be managed with nonsteroidal anti-inflammatory drugs (NSAIDs), a few may develop intense pain requiring dose adjustment or drug discontinuation.[36]

Melanocytic changes seen with BRAF inhibitors include activated nevi, regression, second primary melanomas, and atypical melanocytic proliferations and hence these patients should have regular monitoring of their melanocytic lesions.[33–35] Milia and infundibular occlusion cysts may be seen in up to 25% of the patients on vemurafenib.[39]

Hair changes include alopecia in 8%–36% of patients around 3–15 weeks of starting treatment, increase curling of hair and greying of hair. The alopecia is reversible after stopping treatment.[35,37]

HFS similar to that seen with MKIs may be seen.[34] The combination of an MEK inhibitor trametinib with BRAF inhibitor dabrafenib has been shown to significantly reduce the occurrence of keratinocytic and melanocytic proliferations thus proving the role of paradoxical activation of MAPK pathway with BRAF inhibitors.[40,41]

MEK/ERK INHIBITORS

RAF/MEK/ERK MAPK pathway conducts signals from cell surface to the nucleus and regulates cell survival, proliferation, and differentiation. Activation of MEK/ERK pathway is found in many cancers such as colorectal, pancreatic, NSCLC, hepatocellular carcinomas, and melanomas.[42,43] The adverse effect profile of MEK inhibitors selumetinib and trametinib is more similar to EGFR inhibitors than RAF inhibitors suggesting that inhibition of the MAPK pathway in keratinocytes, either at the level of EGFR or at the level of MEK, causes similar changes. MEK inhibitors have been found to mitigate the adverse effects of BRAF inhibitors when used in combination.[2,42] CADRs to MEK/ERK inhibitors are shown in table 41.6.

Table 41.6: CADRs to MEK/ERK inhibitors (selumetinib, trametinib)

1. Exanthematous morbilliform eruption (46%–74%)[2,33]
2. Papulopustular rash with pruritus[2]
3. Xerosis cutis with erythema[2,33]
4. Paronychia[2]
5. Reduced hair pigmentation[2]
6. Alopecia (17%)[2]
7. Hyperpigmentation[2]
8. Trichomegaly[2]
9. Telangiectasia[2,33]

A papulopustular rash without comedones, similar to that seen with EGFR inhibitors, occurs in over 75% of patients in the second to third week of treatment and follows a similar clinical course.[2] It is distributed predominantly in seborrheic areas and may be associated with pruritus, exudation and crusting.[33,42,44]

An exanthematous morbilliform *rash* is seen in 46%–74% patients. Xerosis and associated pruritus appear early in the course of treatment and may be associated with fissuring of finger tips.[2,33] CADRs seen with EGFR inhibitors may also be encountered.[42,45]

BCR-ABL Tyrosine Kinase Inhibitors

BCR-ABL inhibitors are the oldest targeted inhibitors and act by blocking the tyrosine kinases generated from c-kit, the BCR-ABL fusion protein. Imatinib, nilotinib and dasatinib have been used in chronic myelogenous leukemia, gastrointestinal stromal tumors, dermatofibrosarcoma, Kaposi sarcoma, and melanoma.[3,46] Table 41.7 summarizes some of the CADRs to BCR-ABL tyrosinase kinase inhibitors.

Table 41.7: CADRs to BCR-ABL tyrosine kinase inhibitors (imatinib, dasatinib, nilotinib)

1. Facial edema[3]
2. Generalized pruritic morbilliform rash (7%–21%)[3]
3. Pigmentary changes[3,9]
   a. Patchy and diffuse hypopigmentation
   b. Worsening of preexisting vitiligo
   c. Patchy hyperpigmentation
4. Repigmentation of grey hair[9]
5. Pruritus[9]
6. Acne (dasatinib)[9]
7. Inflammatory eruptions[3,9]
   a. Acute generalized exanthematous pustulosis
   b. Mycosis fungoides–like reaction
   c. Stevens–Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS)
   d. Lichenoid reaction
   e. Pityriasis rosea–like eruption
   f. Psoriasiform dermatitis
   g. Acute neutrophilic eruptions
   h. Pseudolymphoma
   i. Porphyria cutanea tarda
   j. Small vessel vasculitis
   k. Panniculitis
   l. Perforating folliculitis
   m. Erythroderma
   n. Hand and foot syndrome
8. Alopecia—nilotinib

A generalized pruritic morbilliform eruption is seen in 55%–66% of patients on imatinib and about 6% of those on dasatinib, starting around ninth week of treatment. The rash is dose dependent and is more severe in older patients, females and those with smaller lesions.[9,46,47]

Superficial edema has been reported in 48%–65% of patients on imatinib. It is usually localized to the face particularly the periorbital area, rarely associated with pedal edema, pleural effusion, and congestive cardiac failure (1%–3%) with severe weight gain. It is believed to occur as a result of PDGFR inhibition, resulting in increased dermal interstitial fluid pressure. In severe cases, diuretics may be indicated.[3,46,47]

Cutaneous and mucosal lichenoid *reaction* in a dose-dependent pattern has been reported around 1–3 months after initiation of drug, which were managed with topical and systemic corticosteroids.[46,47]

In addition, a variety of inflammatory eruptions have been reported with imatinib as listed in Table 41.8.

Hypopigmentation may be localized and patchy or diffuse, usually more severe in exposed areas. It appears during the first month of treatment, is dose dependent and persists during the treatment. As c-kit and its ligand stem cell factor (SCF) are involved in melanogenesis, proliferation, migration and survival of melanocytes, the inhibition results in reversible hypopigmentation.[46,47] The hypopigmentation is more pronounced in the dark skinned but this is not believed to be an ethnic feature.[9] Treatment includes sun protection, use of broad-spectrum sun screens and tinted cosmetics. Worsening of preexisting vitiligo and repigmentation of previously grey hair has also been described.[9,46,47] Patchy hyperpigmentation has also been reported with imatinib, although the incidence is much lower.[47]

Lobular panniculitis has been reported as a new ADR with dasatinib in patients who were previously on imatinib.[9,47]

PROTEASOME INHIBITORS

Bortezomib is a selective and reversible inhibitor of 26S proteasome that results in inhibition of NF-κB signaling and apoptosis and is used in multiple myeloma with prior treatment failure.[9,48]

The commonest CADR seen with bortezomib is an erythematous to violaceous morbilliform rash with desquamation seen in up to 58% patients.

It usually begins in 10–27 days of starting the drug and is distributed over the face, trunk and extremities. Severe cases may require dose reduction or treatment cessation although majority of cases can be managed with systemic steroids and antihistamines.[9,49]

A bortezomib-induced ***cutaneous vasculitis*** has been described by Gerecitano et al. in 26 of 140 patients, which usually appears in the third or fourth course of the drug. It appears within days of the infusion as an erythematous maculopapular mildly pruritic rash over trunk and proximal extremities which resolves about 5–7 days after last dose of the drug. Histology revealed a perivascular lymphocytic infiltrate with nonnecrotizing vasculitis. A correlation of this rash with treatment response has been suggested.[50]

ANTIANGIOGENIC AGENTS[3]

Neovascularization is crucial to ensure supply of oxygen and nutrition to the rapidly proliferating neoplastic cells. Inhibition of angiogenesis by blockade of VEGF, VEGF tyrosine kinase receptor system and activin receptor-like kinase 1 (ALK-1) is achieved by monoclonal antibodies bevacizumab and ranibizumab. It has been used in metastatic carcinoma of colon, NCSLC, breast cancer and renal cell carcinoma.[3,51]

Because of their effect on endothelial cell proliferation and vascular permeability, VEGF inhibitors cause ***mucocutaneous hemorrhage*** in 20%–40% patients. Mild epistaxis is common but hematemesis, hemoptysis, gastrointestinal bleeding, vaginal bleeding and brain hemorrhage may occur.[51,52] In addition to mild spontaneous mucocutaneous hemorrhage, they can also cause ***serious tumor-related bleeding***. VEGF inhibition also results in ***poor wound healing*** leading to wound dehiscence, bowel perforation, fistula, abscess and hemorrhage.[51,52,53]

It has also been found to produce ***exfoliative dermatitis*** in 3%–19% patients. Gotlib et al. have suggested a positive correlation between skin rash and treatment response.[3,54]

Axitinib, tivozanib and dovitinib are selective VEGFR inhibitors, which have a lower incidence of adverse effects like HFS as compared to MKIs.[55]

P13K-AKT-MTOR PATHWAY INHIBITORS[2,4]

Inhibitors of mTOR act by binding to the immunophilin FK-BP ultimately resulting in G1 phase cell cycle arrest. Three mTOR inhibitors currently in use—rapamycin, temsirolimus and everolimus—have a similar adverse effect profile.[8]

Stomatitis is seen in up to 44% patients early in the treatment and presents as discrete aphthous-like ulceration on nonkeratinized epithelia–like labial and buccal mucosa and the ventral surface of the tongue and floor of the mouth.[14,33] There are distinct, painful, ovoid, grayish-white, superficial ulcers surrounded by a characteristic erythematous margin of <1 cm diameter. It is dose dependent and responds to potent topical corticosteroids although severe cases may require dose reduction or drug discontinuation.[33,56]

A maculopapular rash is seen in 51%–76% patients, which starts within the first few weeks of treatment distributed predominantly on the face and neck and resolves spontaneously at the end of the treatment. Acneiform eruptions, eczematous reaction, xerosis and pruritus have also been reported.[9,33,56]

Nail involvement is seen in the form of paronychia and pyogenic granuloma-like lesions.[33]

HEDGEHOG SIGNALLING PATHWAY INHIBITORS

Vismodegib is a novel inhibitor of Hedgehog signaling pathway, which acts by inhibiting the smoothened (SMO) homologue and is used in locally advanced and metastatic basal cell carcinoma.

The two main CADRs described are alopecia (60%–65%) and dysgeusia (51%).[57] Severe alopecia is seen in 10%–14% patients but is typically reversible. Topical minoxidil has been shown to shorten the duration of hair loss.[33]

Two cases of new onset keratoacanthoma have been reported following the use of vismodegib, although a causal relationship was not established.[58] Other adverse effects seen are muscle spasms (68%), nausea and fatigue.[59,60]

CONCLUSION

The era of targeted therapy has introduced a plethora of drugs into the oncologic armamentarium. These group of drugs produce cutaneous adverse effects that must be recognized early by the treating clinician and the dermatologist. Since these reactions are unique and are florid enough to affect quality of life of these patients, an early recognition is essential. Appropriate treatment decisions in the form of cessation of drug or lowering of the drug dosage are warranted when such reactions are encountered.

LEARNING ESSENTIALS

- With increasing use of specific targeted therapies, the medical community is entering in to hitherto uncharted territory. Clinicians may not be familiar with complete spectrum of toxicity of these agents as they closely mimic a wide variety of inflammatory and neoplastic dermatoses.
- Targeted therapy offer an advantage of acting precisely at the intended target site, but are not devoid of toxicities.
- Skin and skin appendages are a common site of toxicity to these agents that may significantly impair the quality of life and necessitate dose reduction or interrupt the treatment.
- These agents can produce toxicities that may be class specific or unique to an individual agent.
- Papulopustular eruptions, hair and nail abnormalities, xerosis and pruritus are some of the common CADRs to EGFR inhibitors.
- Painful hand foot skin reaction and seborrheic dermatitis-like rash to multikinase inhibitors; facial edema and pigmentary abnormalities in skin and hair to BCR-ABL tyrosine kinase inhibitors; epidermal neoplasms to BRAF inhibitors; alopecia and skin tumors to Hedgehog signaling pathway inhibitors and inflammatory skin rash and peripheral neuropathy to proteasome inhibitors are some of the well recognized toxicities.

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Chapter

42

Adverse Drug Reactions to Topical Dermatology Therapy

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SUMMARY

Adverse reactions to topical dermatology therapeutics are frequent and can either be limited to the skin or can occasionally be systemic as well. Cutaneous side effects may reflect the individuals' intolerance or allergy to the agents. Cutaneous manifestations common to most topicals are contact reactions—irritant, allergic, urticarial, or photosensitive. Other cutaneous adverse reactions could be atrophy, pigmentary alterations, etc. that may be specific to individual topical agents. Topical agents can induce, modify, and even paradoxically aggravate dermatoses for which they were primarily administered. The systemic effects may be indicative of either systemic toxicity or systemic hypersensitivity reactions following percutaneous absorption of the drug. This chapter describes in detail the range of cutaneous and systemic adverse reactions to various topical agents.

INTRODUCTION

Dermatologists have the distinctive advantage of treating many conditions in a targeted manner using topical therapy. This ensures greater concentration of the drug localized at the site of the disease thereby reducing systemic side-effects. Optimal management of a dermatosis using a topical medication is not only determined by the optimal concentration of the drug but also by the appropriateness of other components of the topical preparation, quantity, frequency of application, and duration of use. Adverse effects to topical therapeutics arise either due to individual's inherent sensitivity to the component(s) of the formulation, or to any aberration in the above determinants. As with any therapeutic preparation, adverse reactions to topical therapeutics can either be anticipated or idiosyncratic.

COMPONENTS OF TOPICAL PREPARATIONS CAUSING REACTIONS

The major components of a topical therapeutic are *the drug (active ingredient)* intended to treat the disease and *the vehicle* into which the drug is dispensed. Other *inactive ingredients* making up a topical formulation are preservatives, emulsifiers, absorption enhancers, and fragrances in some (Table 42.1).[1,2] Adverse reactions may occur to any one or more of these components.

ADVERSE CUTANEOUS EFFECTS TO TOPICAL AGENTS

Adverse effects to topical agents can be attributed to host's sensitivity to the medications (contact reactions) or to the inherent properties of these agents. Furthermore, topical therapeutics may induce and/or exacerbate certain dermatoses (e.g. drug-induced acne), and paradoxically induce or worsen the condition for which they are employed.

CONTACT REACTIONS

Contact reactions are by far the commonest adverse effects of topical agents. These can occur in the form of irritant or allergic contact reactions, photosensitive contact reactions, and contact urticaria.

Irritant Contact Reactions

These are nonimmunological, dose/concentration-dependent caustic reactions occurring after application of the topical agent. Clinical manifestations range from mild erythema to overt cutaneous necrosis and scarring, usually confined to the site of contact (Fig. 42.1). Such reactions are more common with topical

Table 42.1: Components of topical preparations

Component	Role
Drug	The active pharmacological agent.
Vehicle	Commonly employed vehicles include creams (water and lipids), ointments (lipids, e.g. petrolatum, cetyl alcohol, lanolin, stearyl alcohol), lotions (water, alcohols), gels (high-molecular weight polymers, e.g. carboxypolymethylene, methylcellulose), powders (talc, starch), paints (water, water + alcohol or alcohol [tinctures]). The choice of vehicle mainly depends on the type of the disease, body site involved and extent of affection.
Emulsifiers	Emulsifiers are used to produce a stable emulsion (oil-in-water or water-in-oil) which are large molecules with both water and lipid soluble properties which allows the topical preparation to bridge the gap between polar and nonpolar substances. Commonly employed emulsifiers include alkyl sulfates and sulfonates, lanolin and its derivatives, glyceryl monostearate, polyethylene glycols, propylene glycol, fatty acid esters, and quaternary ammonium compounds.
Preservatives	Preservatives are required for water-containing preparations (lotions, gels, and oil-in-water creams) as they are easily contaminated by bacteria and fungi. Commonly used preservatives include parabens, hydroxybenzoates, chlorocresol, sorbic acid, propylene glycol.
Absorption enhancers	These agents enhance penetration of the therapeutic agent in the topical preparation, usually by increasing the hydration of stratum corneum or keratolysis. Propylene glycol, urea, salicylic acid, azone, and dimethylsulfoxide are some of the examples.
Fragrances	These substances are mainly used to make the topical preparation more appealing and acceptable to the patient. Cinnamic alcohol, cinnamic aldehyde, eugenol, isoeugenol, geraniol, α-amyl cinnamic alcohol, hydroxycitronellal, and oak moss absolute are some of the examples.

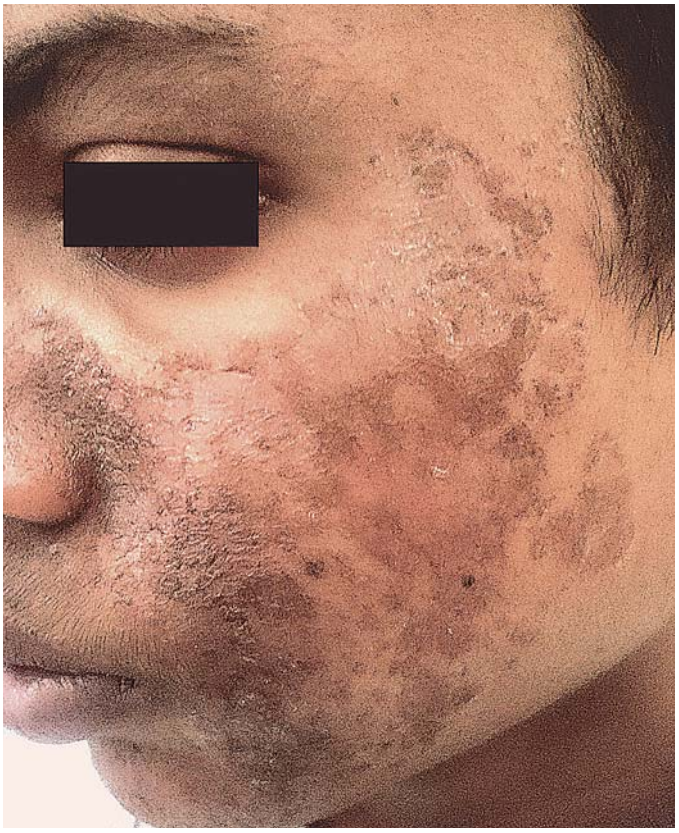

Fig. 42.1: Irritant contact reaction to topical tretinoin creme.

preparations that are inherently irritant in nature (e.g. anti-acne medications, topical cytotoxic agents, demelanizing agents) and/or those containing irritant substances (e.g. acetone, propylene glycol, sodium lauryl sulfate).[3,4] Irritant reactions occur much more readily when the skin barrier is compromised (e.g. in presence of erosions, ulcers, or atrophied skin) and when topical agents are applied on certain areas of the body such as the mucosa, scrotum and eyelids due to more permeable topography at these sites. Table 42.2 lists the topical agents known to cause irritant contact reactions based on the frequency. Certain topical agents (e.g. alcohol-based preparations) also cause *chronic cumulative irritant reactions* following repeated exposure to low concentrations of such agents.[4] This form of reaction, however, is different from the *delayed irritant responses* associated with certain agents (e.g. retinoids, 5-fluorouracil, calcipotriol, etc.) occurring after a few days or weeks of exposure. Irritant reactions can also manifest as acneiform eruptions, urticaria, folliculitis, papulopustular and eczematous lesions.[5]

Allergic Contact Reactions

These are delayed-type hypersensitivity reactions that develop in sensitized individuals. The sensitization generally takes a couple of weeks following initial exposure depending on the ability of the molecule to penetrate into the skin and trigger the immunological cascade. Subsequent exposures, independent of dose/concentration, will lead to development of cutaneous reactions clinically characterized by erythema, edema, vesiculation in the acute form and pruritic lichenified plaques in chronic form. The reaction

Table 42.2: Topical therapeutics causing irritant contact reactions

Class	Frequency		
	Frequent	***Less frequent***	***Occasional***
Retinoids and anti-acne agents	Tretinoin Benzoyl peroxide Adapalene Tazarotene	Clindamycin Erythromycin Azelaic acid	Metronidazole Dapsone Alitretinoin
Antibacterials		Mupirocin (due to the vehicle polyethylene glycol) Retapamulin	
Antiseptics	Povidone iodine		
Antifungals			Clotrimazole Clotrimazole Ketoconazole Terbinafine Ciclopirox olamine
Antivirals		Cidofovir (when used at higher concentrations)	Imiquimod (when used under occlusion)
Cytotoxic drugs	Podophyllotoxin 5-fluorouracil Bleomycin Carmustine	Nitrogen mustards Vinca alkaloids	
Caustics and chemical peeling agents	Salicylic acid Trichloroacetic acid Glycolic acid Phenol		
Inactive ingredients of topical preparations	Propylene glycol Alcohol Acetone Sodium lauryl sulfate Benzoic acid Lactic acid Cinnamic acid compound Urea Formaldehyde Sorbic acid		
Others	Capsaicin Anthralin Antiperspirants (e.g. aluminum chloride) Dithranol	Tacrolimus Pimecrolimus Calcipotriene Sunscreens Hydroquinone Kojic acid Topical anesthetics	Tar Diclofenac gel Minoxidil

may be confined to the site of contact or extend beyond, at times enough to produce erythroderma. On occasions, the site of the dermatitis may be away from the site of contact to the allergen (*ectopic dermatitis*) which will be totally free of any rash (e.g. nail lacquer allergy manifesting as eyelid dermatitis). Allergic contact reactions to topical preparations can be due to the active ingredient or more commonly to the preservatives, fragrances, or other secondary components. Cross-reactivity to structurally related compounds is also possible. Although, any topical agent can induce allergy, the most common agents include antibiotics like aminoglycosides, anesthetics, preservatives, and antihistamines. Allergic contact

dermatitis to topical corticosteroids is also not uncommon and manifests as worsening of the disease with continued application. This typically develops in the setting of stasis eczema which is an important predisposition to develop sensitization to many other topical agents as well.[6–8] Atopic dermatitis is another well-recognized predisposition. Hydrocortisone, budesonide, and hydrocortisone butyrate were shown to be common sensitizers in a series.[9] Topical corticosteroids may cross-react with other steroids based on which they have been grouped into five categories (Table 42.3).[10] Table 42.4 lists the common and most notorious topical agents causing allergic contact reactions. Diagnosis is established by patch testing which however, only demonstrates whether an individual is sensitive to a particular agent and not whether the agent is the cause of dermatitis, as certain individuals who test positive for an agent do not develop reactions even after repeated exposures (e.g. the paraben paradox).[8]

Table 42.3: Topical steroids cross-reactivity groups

Group	Group members	Patch test representative	Group cross-reactivity
Hydrocortisone type (Class A)	Hydrocortisone Tixocortol pivalate Cortisone acetate Hydrocortisone acetate Methylprednisolone Prednisolone Prednisone	Tixocortol pivalate	Class D2
Triamcinolone acetonide type (Class B)	Triamcinolone acetonide Budesonide Amcinonide Desonide Fluocinonide Fluocinolone acetonide Halcinonide Triamcinolone diacetate	Budesonide	Budesonide specifically cross reacts with class D2
Betamethasone type (Class C)	Betamethasone Betamethasone sodium phosphate Clocortolone pivalate Desoximetasone Dexamethasone Dexamethasone sodium phosphate Fluocortolone		
Betamethasone dipropionate type (Class D1)	Betamethasone dipropionate Clobetasol-17-propionate Clobetasone-17-butyrate Alclometasone dipropionate Betamethasone valerate Diflorasone diacetate Fluticasone propionate Mometasone furoate	Clobetasol-17-propionate	
Methylprednisolone aceponate type (Class D2)	Hydrocortisone-17-butyrate Hydrocortisone butyrate Hydrocortisone-17-valerate Prednicarbate Methylprednisolone aceponate	Hydrocortisone-17-butyrate	Class A and budesonide

Table 42.4: Topical therapeutics causing allergic contact reactions

Class	Sensitizing potential	
	High	***Low***
Antibiotics	Bacitracin Neomycin	Fusidic acid Silver sulfadiazine Polymyxin B* Gentamicin* Retapamulin
Anti-acne agents		Benzoyl peroxide Erythromycin
Cytotoxic agents		5-fluorouracil Nitrogen mustards
Contact sensitizers#	Diphenylcyclopropenone Squaric acid dibutyl ester Dinitrochlorobenzene	
Anesthetics	Benzocaine	Prilocaine EMLA$ (lidocaine + prilocaine) Dyclonine
Antihistamines	Ethylenediamine Promethazine Pheniramine Mepyramine maleate	Diphenhydramine
Inactive ingredients of topical preparations	Paraben Formaldehyde Para-aminobenzoic acid Ethylenediamine Fragrances	Propylene glycol Sorbic acid Cetyl alcohol Stearyl alcohol
Others		Minoxidil Triclosan Chlorhexidine Calcipotriene Metronidazole Salicylic acid Wood tar

* Individually demonstrate low sensitizing potential however they are commonly attributed to allergic contact dermatitis owing to cross-reactivity with other aminoglycosides.
\# Therapeutic effect is exerted by sensitization and hence high sensitization potential is a prerequisite for these agents.
$ EMLA - eutectic mixture of local anesthetic.

Photosensitive Contact Reactions

Photosensitive contact reactions occur with those formulations (Table 42.5) and/or their metabolites that accumulate in the skin as photosensitizers absorbing ultraviolet (UV) radiation, most frequently the UVA wavelength, and activating the immunological cascade. Such reactions can be *phototoxic* or *photoallergic*. Phototoxic reactions are more frequent and their severity is dependent on the dose/concentration of the offending agent and occurs without prior sensitization. Phototoxic damage to the tissues can be mediated by *photodynamic reactions* which are associated with generation of free radicals and reactive oxygen species or by *nonphotodynamic reactions* wherein the excited photosensitizers effect tissue damage by directly binding to the cells, inducing pro-inflammatory mediators, or by inducing keratinocyte apoptosis. Photoallergic reactions on the other hand are type IV hypersensitivity reactions which are less common and occur only in sensitized individuals in a dose/concentration independent manner. Photoallergic reactions are diagnosed by photopatch testing.

Table 42.5: Topical therapeutics causing photosensitive contact reactions

Class	Phototoxic	Photoallergic
Antibiotics	Erythromycin	
Nonsteroidal anti-inflammatory drugs	Ketoprofen	Piroxicam Meloxicam Benzophenone Ketoprofen
Photosensitizers	Psoralens* Aminolevulinic acid Methyl aminolevulinic acid Coal tar	Coal tar
Anesthetics	Benzocaine	
Antihistamines	Promethazine	Promethazine Mequitazine
Dyes	Eosin Methylene blue	
Anti-acne medications	Benzoyl peroxide Tretinoin Dapsone	
Sunscreens		Benzophenone-3 Para-aminobenzoic acid Cinnamates Salicylates
Corticosteroids	Hydrocortisone	Hydrocortisone
Antivirals		Aciclovir
Others	Calcipotriene Glycolic acid$	Halogenated salicylanilides Musk ambrette Permethrin#

* Unlike with others, phototoxicity to psoralens appears about 24 h later peaking at 48–72 h following UV exposure.
$ Shown to increase sensitivity to UV light by unknown mechanisms.
# Cross-sensitivity in *Composite* allergic individuals.

Clinically, phototoxic reactions resemble sunburns, ranging from mild erythema to frank necrosis of the skin following exposure to UV light and develop within minutes to hours of exposure in most of the cases. The lesions are usually confined to the site of exposure. Sunburn-like reaction to topical psoralen is a classic example of contact phototoxic reaction. Photoallergic reactions resemble eczematous reactions and typically develop after an interval ranging from hours to days of the drug and UV exposure. The lesions are usually confined to the exposed areas but may be seen extending beyond the site of application as well. Cross-reactivity to chemically identical molecules is also a feature of photoallergic reactions. Occasionally, for reasons unknown, photoallergic reaction may persist even after removal of the offending agent which may clinically evolve over time into chronic actinic dermatitis. This phenomenon has particularly been attributed to topical agents.[11,12]

Contact Urticaria

Contact urticaria can be a manifestation of irritant contact reactions (*nonimmunological contact urticaria*) as a result of profound mast cell stimulation and degranulation. It is generally limited to the site of exposure and severity is dose/concentration dependent. *Immunological contact urticaria* however is an immediate type hypersensitivity reaction occurring in previously sensitized individuals. The lesions may be limited to the site of contact, extend beyond as generalized urticaria with or without angioedema, or manifest as anaphylactic shock as well. Contact urticaria is frequently due to the vehicles and preservatives present in the topical formulations and Table 42.6 lists the most notorious ones.[13,14]

DRUG-SPECIFIC ADVERSE CUTANEOUS REACTIONS

Cutaneous Atrophy

Cutaneous atrophy and striae are the hallmark adverse effects of corticosteroids. Skin atrophy associated with topical steroids is determined by several factors as outlined in Table 42.7. It is important however to note that the potency of a

Table 42.6: Topical agents frequently causing contact urticaria

Contact urticaria	***Nonimmunologic***	Acetic acid, alcohols, balsam of Peru, benzoate, cinnamate, formaldehyde, sodium benzoate, sorbate
	Immunologic	Acrylic monomer, alcohols, ammonia, benzoate, benzophenone, formaldehyde, diethyl toluamide, parabens, polyethylene glycol, polysorbate 60, salicylate, sodium sulfide

Table 42.7: Factors determining the atrophogenic potential of topical steroids

Determinants		Remarks
Corticosteroid-related	Potency	Higher the potency more is the atrophogenicity.
	Frequency	Repeated applications increase the risk of skin atrophy even with mid-potent steroids.
	Duration	Prolonged use increases the risk of cutaneous atrophy.
	Occlusion	Topical steroids under occlusion is advocated in certain situations aiming to enhance percutaneous absorption which is also increases the risk of cutaneous adverse effects.
Host-related	Age	Extremes of age are more predisposed to cutaneous adverse effects of topical steroids as the permeability of the skin in general is more due to underdeveloped skin barrier in neonates and senile atrophy in elderly.
	Body site	Body sites like scrotum, eyelids, axilla, and groins are more permeable and hence more predisposed to develop atrophy compared to rest of the body.

topical steroid is not only determined by the class of the molecule but also by the vehicle which it is dispensed through. Hence, a mid-potent steroid *ointment* may be as atrophogenic as a potent steroid *cream*. Ultrasonography and confocal scanning microscopy are employed to assess the atrophogenicity of topical steroids.[15–17]

Atrophy affects both the epidermis and dermis. Epidermal atrophy initially manifests as decrease in the stratum corneum cell size presumably due to reduced biosynthesis of the cellular macromolecules. With continued application, the keratinocyte number decreases owing to the antiproliferative effects of steroids along with reduction in intercellular lipids and keratohyalin granules. Dermal atrophy is effected by inhibition of secretion of collagen and hyaluronic acid by dermal fibroblasts as well as by the antiproliferative effects on fibroblasts themselves. The combined atrophogenic effects on epidermis and dermis manifests in the early stages as wrinkled shiny skin with striae, purpura, and telangiectasia. Later, hematomas and small lacerations develop due to loss of dermal vasculature support and increased skin fragility. Corticosteroid-induced striae develop rapidly over the body folds and in contrast to striae distensae, are larger, wider, erythematous, and often pruritic (Figs. 42.2 A and B). Atrophic changes resolve in about 4 weeks of discontinuation of steroids but can be irreversible. Striae are permanent.[14–16]

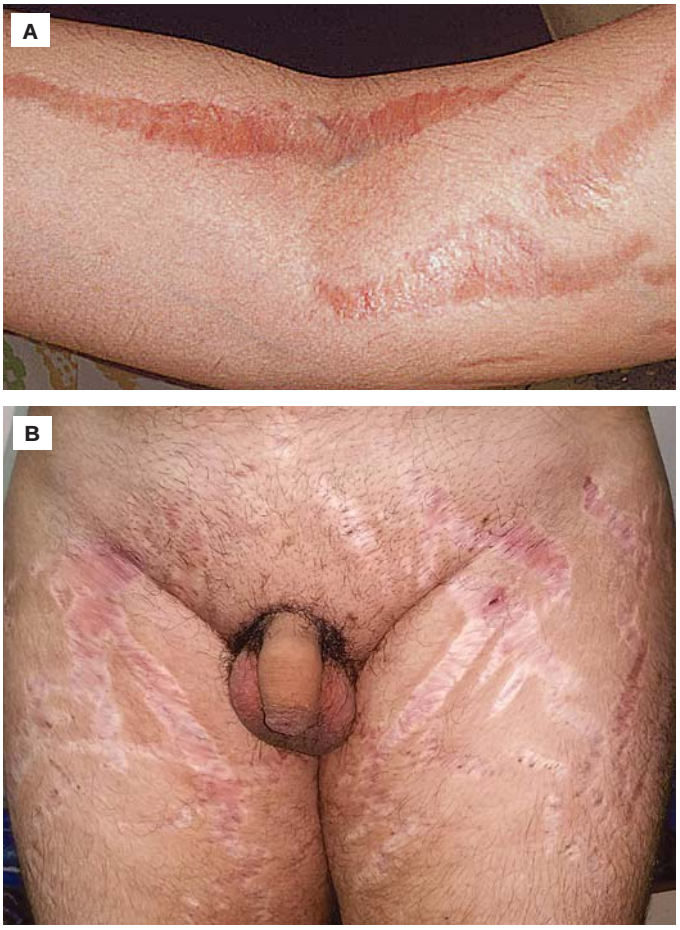

Fig. 42.2: Steroid induced striae involving the arm (A); the pubic region and the upper thighs (B).

Cutaneous Dyschromatosis

Cutaneous pigmentary alterations as adverse effect of topical agents occur with many drugs. The pigmentary changes can assume different morphological patterns depending on the underlying mechanism. They can be broadly grouped into *hyperpigmentation* and *hypo- or depigmentation*. Hyperpigmentation can be either postinflammatory, due to increased melanogenesis, or due to deposition of drugs and/or their metabolites in the skin as outlined in Table 42.8. The classical example of the latter is exogenous ochronosis (Figs. 42.3A and B) caused by prolonged use of hydroquinone.[8] It is likely due to inhibition of dermal homogentisate oxidase by hydroquinone leading to polymerization of homogentisic acid and its deposition in dermis as ochronotic pigment. Histopathology demonstrates ochre-colored, "banana-shaped" fibers within the upper dermis. Hypo- or depigmentation occurs as a result of either destruction of melanocytes or due to reduced melanogenesis. Melanocytotoxic depigmentation can be a postinflammatory phenomenon following contact reactions or effected specifically by aromatic and aliphatic phenol derivatives. These are structurally similar to tyrosine and are converted by tyrosinase-related protein 1 to melanocytic destructive reactive oxygen species leading to contact/chemical leukoderma. Steroid-induced depigmentation (Fig. 42.4) is frequently encountered with fluorinated steroids and is possibly due to inhibition of melanogenesis. Other pigmentary derangements are outlined in Table 42.8.[17-21]

Hypertrichosis

Hypertrichosis of the forehead and temples in patients using topical minoxidil for androgenetic alopecia is not uncommon and rarely generalized hypertrichosis due to systemic absorption is also possible.[22,23] However, topical steroid abuse over the face is associated with hypertrichosis, a commonly dealt adverse effect which is irreversible on discontinuation (Fig. 42.5). Acquired hypertrichosis is attributed to other topical agents such as latanoprost and psoralens. The former is a topical prostaglandin analogue used in treatment of glaucoma and is known

Table 42.8: Topical therapeutics causing cutaneous dyschromatosis

Pigmentary alteration	Pathomechanism	Drugs implicated	Specific morphology
Hyperpigmentation	Melanocytotrophic	Postinflammatory	
	↑Melanogenesis	Bleomycin	Flagellate hyperpigmentation
		Psoralens	
	Deposition	Hydroquinone	Blue-black (Exogenous ochronosis)
		Silver sulfadiazine	Slate grey (Argyria)
Hypo or depigmentation	Melanocytotoxic	Hydroquinone Monobenzyl ether of hydroquinone *p*-tert-Butylcatechol *p*-tert-Butylphenol *p*-tert-Amylphenol Cinnamic aldehyde *p*-phenylenediamine Benzyl alcohol Azelaic acid	Hypo- or depigmentation induced by these agents is termed "contact/ chemical leukoderma" which in contrast to vitiligo vulgaris may shows satellite depigmentation.
		Imiquimod Chloramphenicol eye drops	Poliosis
		Diphenylcyclopropenone	Sometimes both hyper and hypopigmentation occur in a typical pattern referred to as "*dyschromia in confetti*".
		Chemical peels	
		Postinflammatory	
	↓ Melanogenesis	Corticosteroids	May be poikilodermatous.
		Topical prostaglandin $f_{2\alpha}$ analogues	Poliosis
Staining		Potassium permanganate Silver nitrate Dithranol Povidone iodine Gentian violet Tetracyclines	

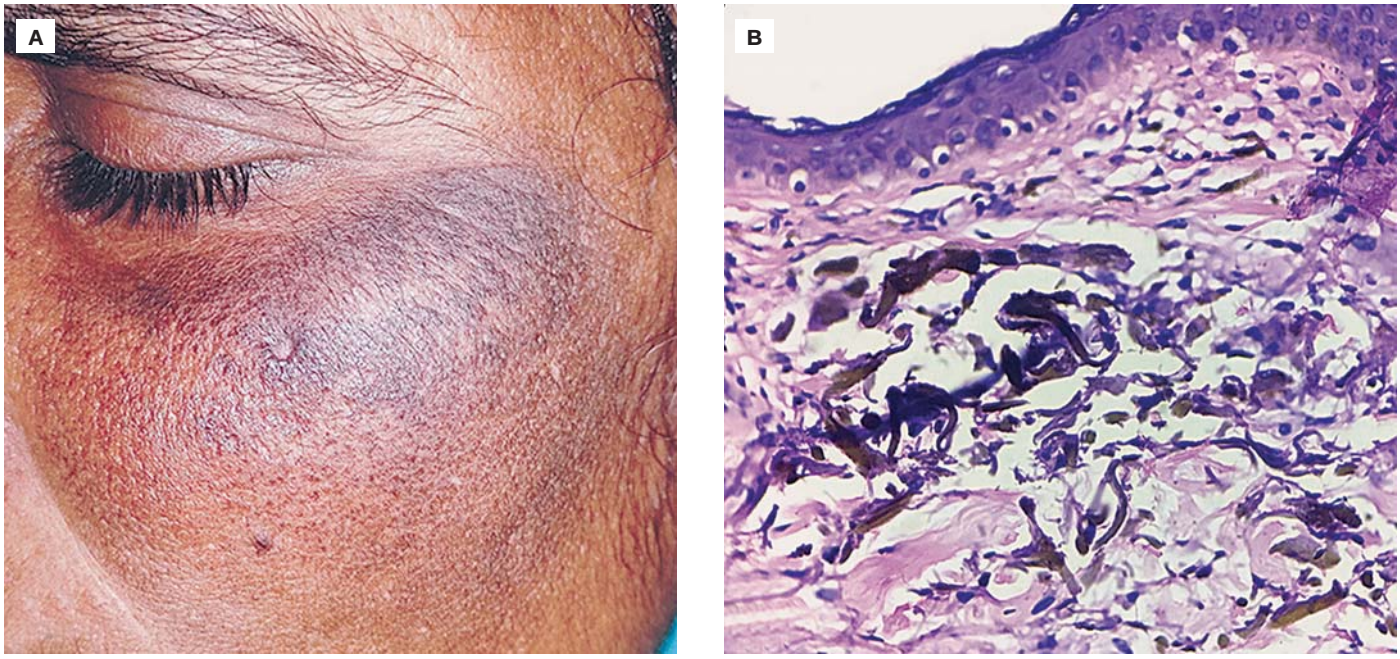

Fig. 42.3: (A) Exogenous ochronosis on face, due to prolonged use of hydroquinone crème; (B) Histopathology of the same patient showing typical ochre bodies in dermis.

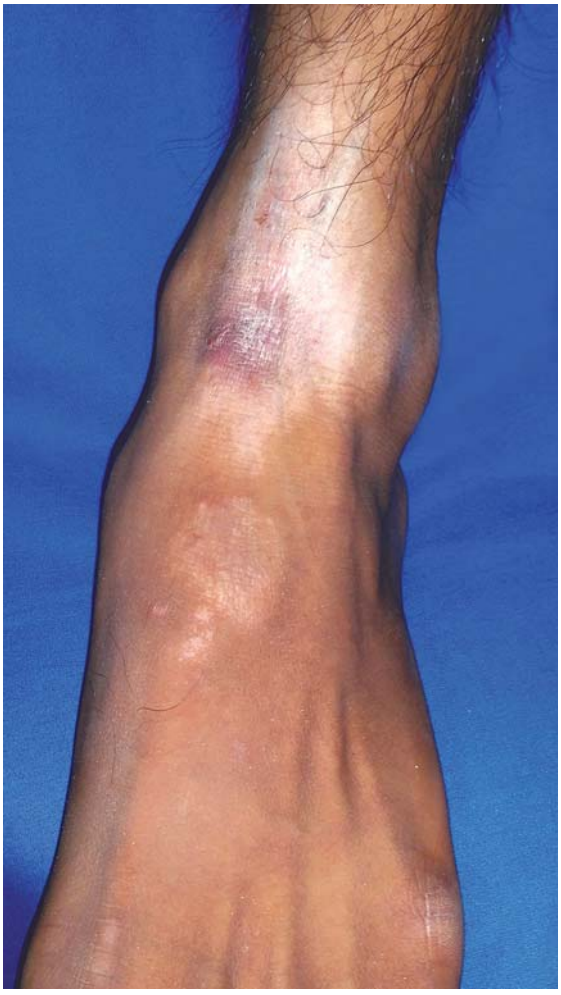

Fig. 42.4: Steroid-induced depigmentation due to use of potent steroids.

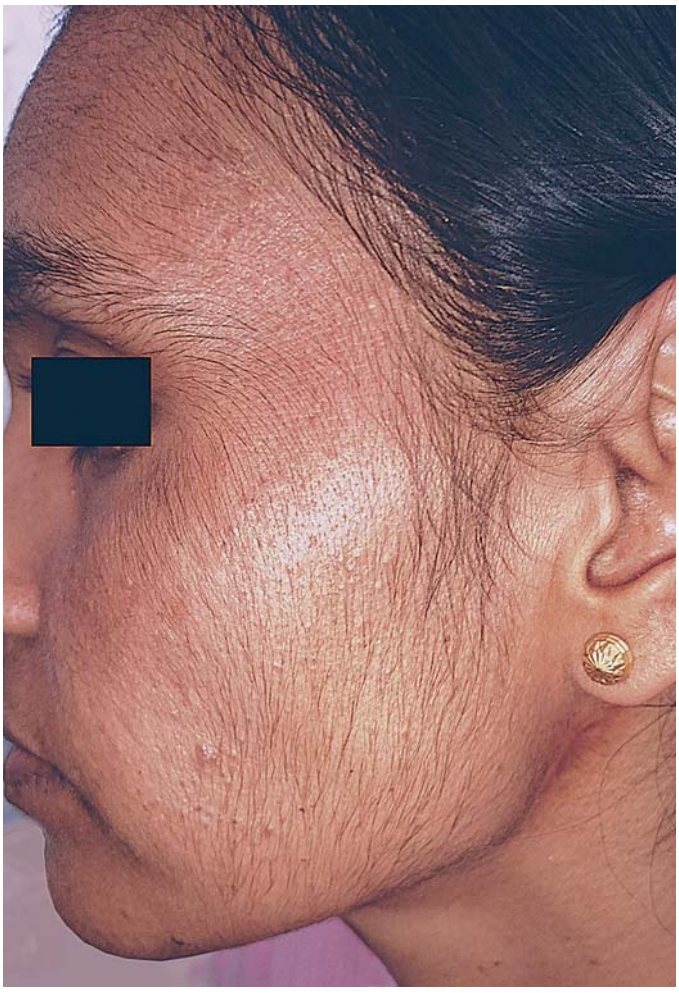

Fig. 42.5: Steroid-induced hypertrichosis on the face due to prolonged use of mometasone.

to produce localized hypertrichosis of eyebrows and eyelashes presumably by increasing the cell division and metabolism. Psoralens can induce transient hypertrichosis over the sun-exposed areas.[24]

Nail Changes

Onycholysis and permanent nail dystrophy have been observed with intralesional bleomycin therapy.[25] Periungual pain, erythema, and edema may develop as an allergic contact reaction to nail lacquers. Wet nail lacquers are known to produce allergic reactions more frequently compared to dry ones.[26] Photodynamic therapy on hands and fingers has been shown to produce onycholysis, photo-onycholysis, and nail plate discoloration.[27] Staining of nails occurs with tar, anthralin and other therapeutic dyes.

Telangiectasia

Most common topical agents causing telangiectasia are the corticosteroids attributed to the stimulation of dermal vascular endothelial cells to proliferate as well as stimulation of release of nitric oxide by the endothelial cells causing vasodilatation. The telangiectasias (Fig. 42.6) resolve with discontinuation of steroids. "Facial plethora" or rebound vasodilatation following discontinuation of topical steroids is another characteristic feature of steroid abuse which compels the patients to reuse the steroids to gain relief leading to a state of steroid addiction. Nitric oxide is again implicated in this vasodilatation. Benign telangiectasias occur as a common adverse effect of topical carmustine used in cutaneous mycosis fungoides. They usually resolve following discontinuation of the drug over variable period of time but may remain persistent.[21,25,28]

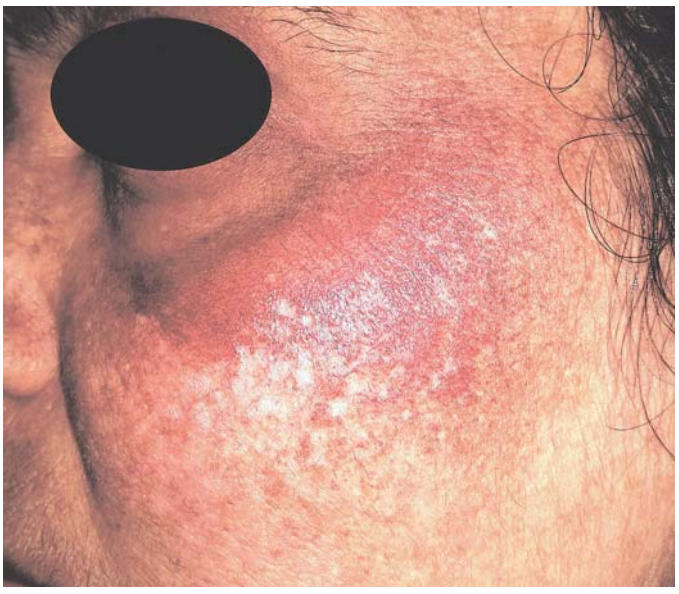

Fig. 42.6: Steroid induced telangiectasia and rosacea on face.

Cutaneous Ulceration

Any topical medication can produce cutaneous ulceration when the irritant contact reaction developed toward it is severe enough. However, certain drugs can themselves be inherently ulcerogenic. Topical steroid-induced skin ulceration (steroid ulcers) is seen with long-term application of potent steroids, especially over the skin with diminished perfusion (e.g. venous ulcers).[29] Clinically, they are characterized by indolent, punched out ulcers with greyish slough (Fig. 42.7) and are attributed to their vasoconstrictive properties. Topical imiquimod has been shown to induce ulceration as a contact reaction not only at the site of application but also at distant sites possibly due to overwhelming cytokine-mediated proinflammatory response.[30–32] Topically applied podophyllin for genital warts can induce ulcers. Neonates developing periocular ulcerative dermatitis after the use of gentamicin ointment for ocular infection prophylaxis has also been reported.[33]

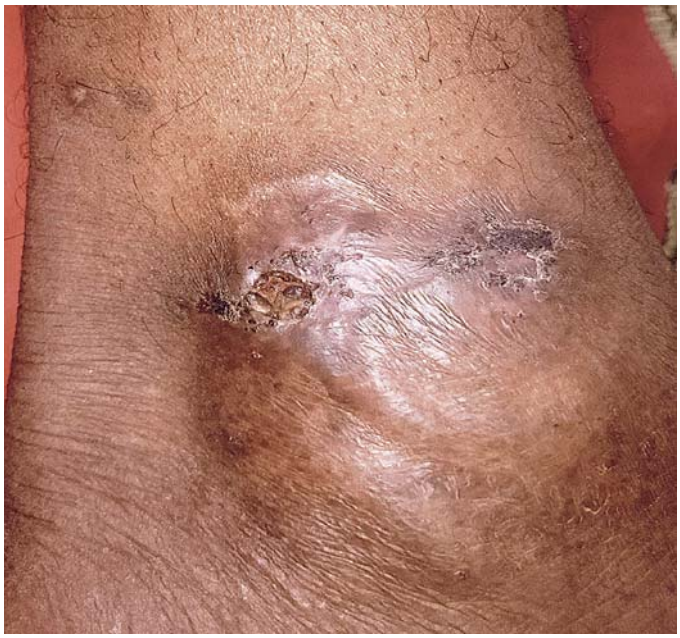

Fig. 42.7: Steroid ulcer on ankle.

INDUCTION/REACTIVATION/ALTERATION OF DERMATOSES

Acne

Corticosteroids (topical, inhaled, or systemic) are the commonest cause of drug-induced acneiform eruptions which develop as early as after 2 weeks of steroid use. High-potency steroids, proneness of individuals to develop acne, and application of the steroids at acne-prone areas predispose to development of steroid acne (Fig. 42.8). Degradation of follicular epithelium with its consequent extrusion

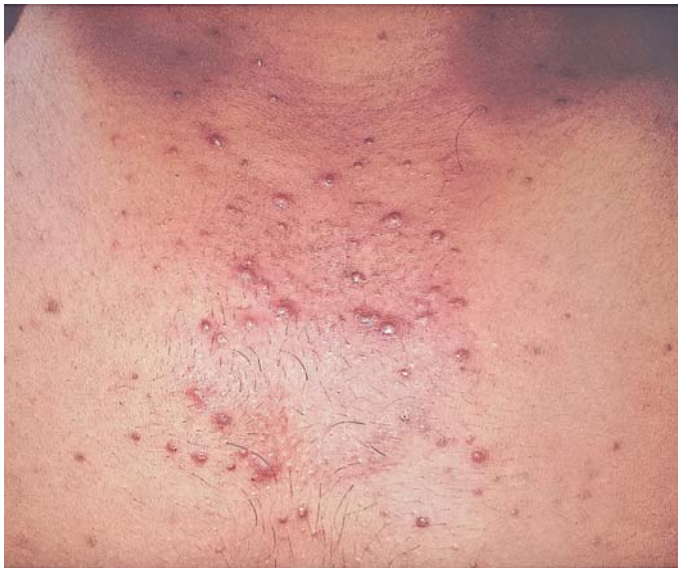

Fig. 42.8: Steroid acne on trunk due to the use of superpotent steroid creme.

is implicated in steroid acne.[21] Also, inadvertent application of steroids for acne vulgaris worsens the disease. Apart from topical steroids, topical calcineurin inhibitors,[34,35] tars, sunscreens, chemical peeling agents, cosmetics and pomades have been implicated in drug-induced acneiform eruptions. Acneiform eruptions to sunscreens *per say* is due to the preservatives in the formulation and not due to the active ingredients which although may be oils, are typically noncomedogenic.[36] Cosmetic acne is also due to the various comedogenic preservatives and other inactive ingredients in the preparation most notably lanolin, petrolatum, vegetable oils, butylstearate, lauryl alcohol and oleic acid.[37] Drug-induced acneiform eruptions have certain characteristics which distinguish them from acne vulgaris (Box 42.1).[38,39]

Box 42.1: Characteristics of drug-induced acneiform eruptions

- Sudden onset
- Acute or subacute course
- Appearance at ages atypical for acne vulgaris
- History of topical or systemic medication use
- Monomorphic lesions and lack of comedones (comedones may develop later secondary to inflammatory lesions)
- Involvement of atypical sites (e.g. forearms, buttocks, legs)
- Resistant to conventional treatment
- Onset typically after medication use, improvement after discontinuation and recurrence following subsequent exposure

Occlusion Miliaria

Similar to acne, application of oils or oily creams can cause occlusion of eccrine sweat ducts leading to occlusion miliaria.

Rosacea

Corticosteroids (topical, inhaled or systemic) are the commonest cause of drug-induced rosacea and can both induce or worsen the disease. It frequently occurs in fair-skinned individuals who have been using steroids for long periods (more than 8 weeks). Probable mechanisms include vasodilatation, rebound release of proinflammatory mediators, accumulation of nitric oxide, and diminished local immunity favoring proliferation of *Demodex*. A typical narrative would be an improvement of the disease initially after steroid application but with continued use increased redness, photosensitivity, and irritation to trivial noxious stimuli attributable to atrophy and persistent vasodilatation ensue along with development of erythematous papules (Fig. 42.9). Discontinuation of steroid at this stage leads to rebound flare which compels its reuse which produces prompt albeit transient relief leading to a state of steroid dependency.[40,41] Topical tacrolimus has been found useful for primary as well as steroid-induced rosacea which although may itself paradoxically induce or exacerbate rosacea (see below).

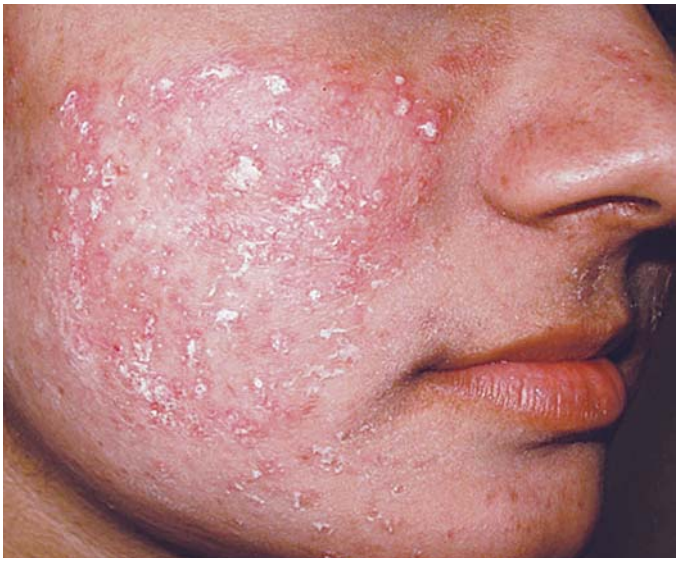

Fig. 42.9: Steroid-induced rosacea in a young girl due to the use of potent steroids on the face.

Perioral Dermatitis

Perioral dermatitis (Fig. 42.10) has been attributed to various infective, allergic, or irritant factors but none of them have been convincing. Only relation to

topical steroids is well established. More potent the steroid more likely is the development of dermatitis even after brief exposures. Systemic and inhaled steroids can also induce the dermatitis. A periocular form similar to perioral dermatitis may develop with steroid eye drops. The lesions initially affect the nasolabial folds characterized by grouped follicular papules, *Demodex*, or pustules on an erythematous background. Later, they spread all around the lips which are conspicuously spared. Treatment involves discontinuation of the steroids which however may cause a flare. Topical or systemic tetracyclines, topical calcineurin inhibitors, metronidazole and photodynamic therapy have been advocated for treatment.[40,42]

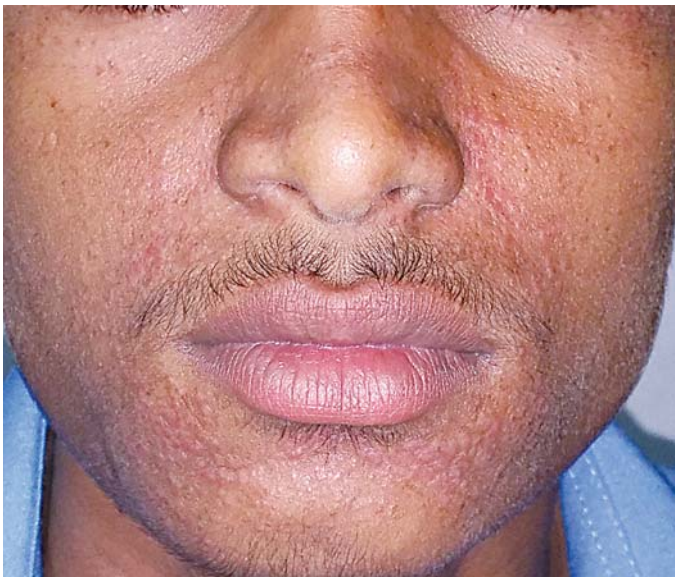

Fig. 42.10: Steroid induced perioral dermatitis.

Trichostasis Spinulosa

Trichostasis spinulosa is a disorder of pilosebaceous units occurring due to hyperkeratosis of the infundibulum of dilated vellus follicles leading to retention of catagen hairs. Clinically, the lesions are characterized by discrete follicular papules which may be pruritic often involving the tip of the nose, neck, upper chest, and back. Dermoscopy reveals retained clumps of hairs within the follicular openings.[43] Topical steroids and minoxidil are implicated in this condition.[44,45]

Infantile Gluteal Granuloma

Infantile gluteal granuloma arises as a complication of topical steroid use, especially the fluorinated ones, in the treatment of primary irritant napkin dermatitis. The lesions appear frequently on the buttocks, groins, lower abdomen and upper thighs as livid-red papulonodules typically aligned in a linear pattern parallel to and sparing the skin folds. Treatment involves discontinuation of steroids and attention to napkin care.[46,47]

Intertriginous Granular Parakeratosis

Intertriginous granular parakeratosis is thought to be an irritant response to antiperspirants and deodorants or to excessive use of soaps and creams. Lesions begin as itchy erythematous to brownish keratotic scaly papules and plaques that coalesce into more verrucous-appearing lesions. Secondary changes such as erosions, vesiculation and maceration develop due to friction. Although classically axillae are involved, other flexures may also be affected.[48] It is speculated that the implicated agents interfere with the processing of filaggrin.[49] The disease derives its name from the typical histopathological features characterized by compact parakeratosis with retention of keratohyalin granules within these parakeratotic cells.[50]

Cutaneous Infections and Infestations

Topical tacrolimus has been attributed to reactivation of herpes simplex and induction of other cutaneous viral infections especially in the setting of atopic dermatitis possibly by diminishing the already attenuated cutaneous immunity.[51-53] Kaposi's varicelliform eruption has also been precipitated by topical tacrolimus in the setting of atopic dermatitis.[54,55] Chemical peels are occasionally associated with reactivation of labial herpes possibly due to increased post-peel photosensitivity even with prophylactic antivirals.[56]

Prolonged use of both oral and topical antibiotics in acne can induce Gram-negative folliculitis due to overgrowth of *Klebsiella*, *Escherichia coli*, *Proteus*, *Serratia* or *Pseudomonas* organisms. Among the topical antibiotics, tetracycline, clindamycin, and erythromycin are the frequently implicated. Clinical presentation may be either an acute pustular flare of the acne or painful deep pustules or nodules which may interconnect and form sinus tracts. Isotretinoin is the drug of choice for Gram-negative folliculitis.[57]

Topical steroids are also implicated in *Malassezia* folliculitis, presenting as pruritic follicular erythematous papules or pustules over the back, upper chest, and shoulders due to overgrowth of the organism consequent to diminished local immunity.[58] Prolonged use of topical steroids also increases the susceptibility to cutaneous bacterial infections. Tinea incognito or steroid-modified dermatophytosis (Fig. 42.11) is rampant due to steroid abuse wherein the primary morphology and symptomatology of the disease are

masked by the anti-inflammatory properties of steroids A similar phenomenon is described with abuse of topical steroids in scabies as well. Even crusted (Norwegian) scabies (Fig 42.12) following long-term treatment with topical steroids is reported.[59]

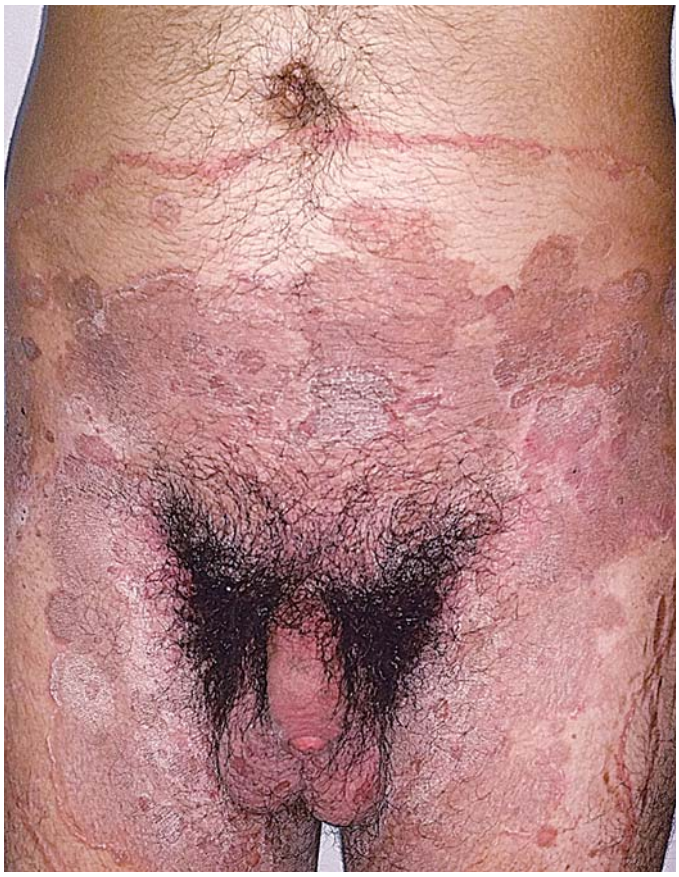

Fig. 42.11: Tinea incognito on abdomen. Note widespread striae on thighs.

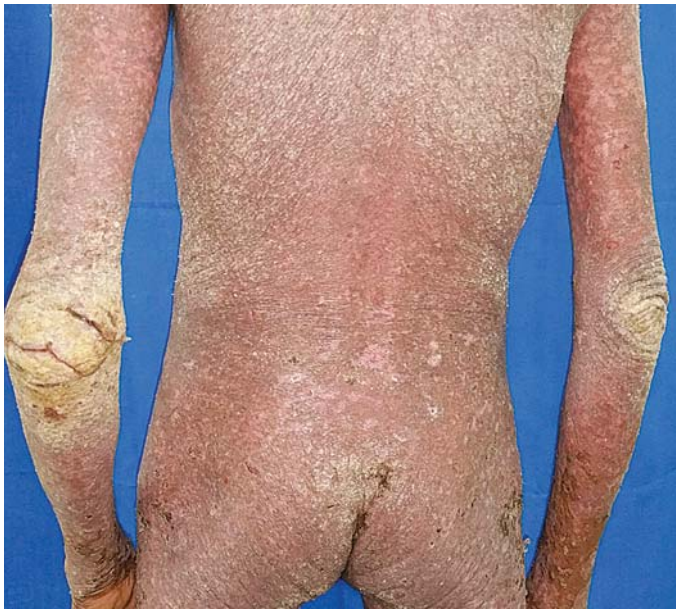

Fig. 42.12: Norwegian scabies in a patient due to prolonged use of potent steroid creme for disseminated dermatitis.

Cutaneous Neoplasms

Certain topical therapeutics have the potential to induce cutaneous neoplasms (benign, premalignant and malignant) due to their inherent immunosuppressive, mutagenic and genotoxic characters. Topical cytotoxic drugs, immunomodulators, contact sensitizers, and photosensitizers are the most notable ones in this regard. Nitrogen mustard has been shown to produce nonmelanoma skin cancers, predominantly squamous cell carcinoma, at an average frequency of 10% when used for mycosis fungoides, especially in the genital area.[60] Old age and photo-damaged skin may predispose to development of secondary malignancies by nitrogen mustard.[61] Although topical calcineurin inhibitors have been found safe in terms of nonmelanoma skin cancer risk, a few reports of lymphoma have been documented with their use. However, the United States Food and Drug Administration found 19 and 10 cases of different malignancies related to topical tacrolimus and pimecrolimus, respectively based on which a public health advisory was issued that suggested the use of these agents to be only as labeled and in those unresponsive to other therapies.[62] New lesions of Kaposi's sarcoma (KS) developed at the site of topical corticosteroids application for erosive lichen planus (LP) in a patient with known erythroblastopenia, thymoma, and KS.[63]

The variable carcinogenic potential of different tars is attributed to the number of carcinogens present in them with coal tar being most carcinogenic due to the presence of polyaromatic hydrocarbons and pyridines.[64] Although cutaneous malignancies, especially genital neoplasms, are only anecdotally documented with long-term use of topical tar, use of tar with ultraviolet radiation as in psoriasis is associated with increased risk of neoplasms though the relative carcinogenic contribution of either is undetermined.[65–67] Tars are also implicated in tar keratoses and keratoacanthoma.[68] As opposed to oral psoralen plus ultraviolet A (PUVA) therapy, there is no evidence of either melanoma or nonmelanoma skin cancer with topical PUVA. However, carcinogenicity with PUVA therapy is possibly determined by the type of psoralen rather than the route of administration, and hence it is only reasonable to believe that the exposure-based carcinogenic risk is same for oral or topical PUVA.[69,70]

PARADOXICAL REACTIONS

Topical Calcineurin Inhibitors Induced Rosacea

Topical tacrolimus and pimecrolimus are effective in treatment of primary as well as steroid rosacea.

However, several cases of rosaceiform dermatitis following long-term use of topical calcineurin inhibitors have also been documented. Immunosuppression leading to overgrowth of *Demodex* mites and the vasoactive properties of these drugs possibly act synergistically leading to rosacea-like dermatitis.[8,71] A severe granulomatous rosacea resistant to oral tetracycline has also been induced by topical tacrolimus.[72]

Acne Flare with Topical Retinoids

An initial transient acne flare, which can be pustular, is noted with topical retinoids frequently requiring no discontinuation of treatment.[73] Whether this flare is due to retinoids or is a natural course of the disease is not clear. Acne flare is rather more common after oral isotretinoin intake. Patients however should be made aware of this beforehand to ensure compliance.[74,75]

Photosensitive Reactions to Sunscreens

Sunscreens can paradoxically produce photosensitivity which fortunately is uncommon. Contact reactions, including photoallergic reactions must be suspected when the pre-existing photosensitive dermatosis worsens with the use of sunscreens. Although the active ingredients can induce sensitization (Table 42.5), photoallergic reactions to sunscreens may also be mediated by the fragrances and preservatives contained in them. Hence, photo-patch testing must be carried out with individual components of the formulation.[76]

Minoxidil-induced Hair Shedding

Patients using topical minoxidil for androgenetic alopecia may complain of diffuse hair fall within the first 4–6 weeks of therapy. It is attributed to the minoxidil-induced premature termination of telogen in responsive follicles that transit to anagen leading to a brief telogen effluvium. Need for patient education regarding this to ensure compliance cannot be overemphasized.[77]

Prostaglandin F2$_\alpha$ Analogues-induced Poliosis

Latanoprost, travoprost, and bimatoprost are topical medications used for glaucoma. They are also of dermatological relevance as they are used to promote growth and darkening of eyelashes and eyebrows. A paradoxical poliosis induced by these agents possibly by inhibition of tyrosinase has also been documented.[18,78]

SYSTEMIC ADVERSE EFFECTS TO TOPICAL THERAPEUTICS

Systemic absorption of topically applied agents always occurs to a variable extent. However, this absorption on most occasions is insignificant enough to cause any systemic effects. Various factors that influence the systemic absorption are listed in Table 42.9. The systemic effects of topical drugs can be broadly grouped into those due to hypersensitivity reactions and those due to drug toxicity. The latter requires systemic absorption to be enough to attain toxic serum levels. The former however is dose-independent.

The most important systemic hypersensitivity reaction to topical medications is generalized urticaria with angioedema or anaphylaxis (Box 42.2). This can be a Type I hypersensitivity reaction in previously sensitized individuals or a manifestation of contact urticaria that can either be immunological or nonimmunological (see above).[79]

Table 42.9: Factors determining the systemic absorption of topically applied agents

Determinants		Remarks
Host-related	Age	Extremes of age are more predisposed to increased absorption of the drug. (High surface area to body mass ratio in children and diminished skin thickness and impaired cutaneous barrier function in elderly.)
	Body site	Scrotum, eyelids, axilla, and groins are more permeable, and hence more amount of drug is absorbed from these sites .
	Skin barrier	Impaired skin barrier function as in atopic dermatitis and erythroderma is associated with increased absorption.
	Underlying disease	Any dermatosis associated with inflammation and/or breach in the epithelium enhances absorption of the drug.
Drug-related	Nature of the drug	Hydrophilic molecules are absorbed to a greater extent, especially on inflamed skin.
	Occlusion	Occlusion enhances absorption of the drug.
	Drug formulation	Ointments, by the virtue of their hydrating effect on the skin are more absorbed compared to e.g. a cream.
	Concomitant use of other topical agents	Emollients that are commonly employed with e.g. a topical steroid in hyperkeratotic disorders enhance the absorption of the drug.

Box 42.2: Common topical agents inducing anaphylactic reaction

- *Anesthetics:* Benzocaine, proparacaine
- *Antibiotics:* Bacitracin, neomycin, chloramphenicol, ampicillin, silver sulfadiazine
- *Others:* Milan's solution, chlorhexidine, ammonium persulfate

The most important systemic effects of concern in dermatology are the ones associated with topical steroids. Suppression of hypothalamo–pituitary axis (HPA), iatrogenic Cushing's syndrome, and growth retardation can occur with topical steroids. Although most of the HPA suppressions show only laboratory abnormalities, many cases with impaired stress responses have also been reported. Alteration in normal glycemic control or even hyperglycemia induced by topical steroids is possible.[80]

Systemic absorption of topically applied salicylic acid is seen when the concentration is 10% or more and when applied to more than half the body surface area, especially when it is incorporated in a hydrophilic ointment or used under occlusion. Clinical signs of salicylism appear when blood concentrations exceed 35 mg/dL. Manifestations include nausea, vomiting, confusion, dizziness, tinnitus, delirium, psychosis, stupor, coma, and death. Marked hyperventilation and respiratory alkalosis are other features. Metabolic acidosis may also occur in children.[64]

Although no evidence of significant absorption of topical retinoids is demonstrated, it is however recommended to completely avoid them during pregnancy.[81] Table 42.10 lists the topical agents that have shown to produce systemic toxicity due to percutaneous absorption.

Table 42.10: Systemic toxicities to topical agents

Drug	Systemic toxicity
Neomycin	Ototoxicity, Nephrotoxicity
Silver sulfadiazine	Hemolysis in glucose-6-phosphate dehydrogenase deficiency Hyperosmolality Methemoglobinemia Argyria
Clindamycin	Pseudomembranous colitis
Bleomycin	Raynaud's phenomenon
Podophyllin	Birth defects intrauterine death Stillbirth
Corticosteroids	Hypothalmo–pituitary axis suppression Iatrogenic Cushing syndrome Growth retardation in children Hyperglycemia
Calcipotriene	Hypercalcemia, Hypercalciuria
Salicylic acid	Salicylism Hypoglycemia
Phenols	Hemolytic anemia Methemoglobinemia Hemoglobinuria

LEARNING ESSENTIALS

- Adverse reactions to topical agents are frequent and can be both cutaneous and systemic.
- Cutaneous adverse effects can be contact reactions including photosensitive reactions, specific drug-related adverse effects, and induction, reactivation, or alteration of certain dermatoses.
- Certain topical agents may paradoxically induce or exacerbate the diseases for which they are used.
- Systemic adverse effects to topical agents may be due to hypersensitivity reactions or due to drug toxicity following percutaneous absorption.

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Section IV: CADRs in Special Situations

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Chapter

43

Cutaneous Adverse Drug Reactions in HIV/AIDS

Yogesh S. Marfatia • Ruchi Shah

SUMMARY

With the availability of potent antiretroviral drugs, HIV/AIDS has become a chronic manageable disease. However, these drugs exhibit various long-term as well as short-term, cutaneous as well as systemic adverse drug reactions (ADRs). ADRs result in discontinuation of drugs, thereby, decreasing patient's compliance and adherence to treatment, leading to potential drug resistance and compulsion to use second-line regimen, which are much more expensive. HIV/AIDS cases are more prone to develop ADRs due to immune dysregulation, genetic and viral factors, polypharmacy, and altered drug metabolism. The cutaneous manifestations serve as an important marker of internal involvement. Among cutaneous adverse drug reactions (CADRs), drug hypersensitivity reactions are the most common adverse reaction to combined antiretroviral therapy (cART), particularly with nevirapine, abacavir and efavirenz. Other manifestations include urticaria, pigmentation (particularly zidovudine), and fatal reactions such as Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and drug rash with eosinophilia and systemic symptom (DRESS) (due to abacavir and nevirapine). Standardized causality assessment is useful for determining the drug responsible for any ADR. Symptomatic and specific treatment can be instituted and the culprit drug should be discontinued. Early detection and treatment of CADRs and identification of the causative agent are essential to prevent the progression of the reaction, preventing additional exposures and ensuring the use of alternative medicines for the current condition. Development of predictive genetic biomarkers and drug molecules having minimum adverse effects is the need of the hour to manage a lifelong infection like HIV/AIDS.

INTRODUCTION

Entry of HIV in the body and its subsequent high-level replication causes resultant immunosuppression. HIV replication is highly error prone, thus increasing the potential for mutation and thereby, resistance.

The virus persists in the body due to its entry in sanctuary sites and resting memory T cells, making HIV a lifelong and incurable infection. With more than 25 FDA-approved drugs comprising of 6 different groups available as of now, it has become a chronic manageable disease. Exposure to combined antiretroviral therapy (cART) has got short-term toxicities and hypersensitivity as well as long-term morphologic and metabolic abnormalities. Many drugs coprescribed for prevention and management of opportunistic infections are known to cause cutaneous and systemic adverse drug reactions (ADRs). In a study of 90 cases on nucleoside reverse transcriptase inhibitor (NRTI) plus non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen, 44.4% cases were reported to have cutaneous adverse drug reactions (CADRs), the most common being nail pigmentation (14.4%), grade I, II, III skin rash (10%), and grade IV [Stevens–Johnson Syndrome (SJS) (3.3%)].[1] Cutaneous manifestations of ADRs are common and easy to diagnose and also serve as a surrogate marker of internal involvement. Dermatovenerologists play a crucial role in identifying and managing ADR.[2] Key to success of cART is the highest possible level of adherence to prescribed regimen (95%). About 80% of patients experience ADRs during treatment, which is the most common reason for discontinuation of cART,[3] Decreased compliance results in drug resistance and need for use of second-line or alternative drugs, which may be expensive.

HIV infected cases are more prone to ADRs because of various factors.[4] Such factors include altered drug metabolism, immune dysregulation, genetic predisposition, polypharmacy, oxidative stress etc. They are elaborated below.

FACTORS INFLUENCING DEVELOPMENT OF ADRs IN HIV/AIDS

Pharmacogenomics

People with different genotypes respond differently to particular drugs. Abacavir hypersensitivity is strongly associated with major histocompatibility complex (MHC) allele, HLA-B*5701.[5] Screening before prescription is recommended in clinical guidelines. Possible relationship between cutaneous hypersensitivity by nevirapine and efavirenz and HLA-DRB101 allele has been noted.[6]

Sex

Higher incidence of SJS and symptomatic hepatic events with nevirapine has been found in female patients.

Patient's Immune Status

ADR manifestations vary with viral load and CD4 count. Hypersensitivity in association with nevirapine occurs more commonly at higher CD4 counts. It is recommended to start nevirapine when CD4 counts are lower than 400 and 250 cells/μL in antiretroviral naive men and women, respectively.[7] In cases on cART with virological suppression, switching to nevirapine above these CD4 thresholds does not necessarily have a greater risk of hypersensitivity. Avoidance of nevirapine in postexposure prophylaxis regimen is essential.

Polypharmacy/Drug–Drug Interactions

Apart from antiretroviral drugs, various other drugs are administered for prophylaxis or treatment of coexisting opportunistic infections thereby increasing potential for drug toxicities and interactions.

ANTIRETROVIRAL THERAPY AND DRUG REACTIONS

HIV-infected cases are more prone to develop hypersensitivity reaction to drugs than general population. They develop symptoms or signs when exposed to a defined drug at dose tolerated by a healthy individual. Pathophysiology of drug hypersensitivity is based on a variety of factors such as immunological, host and viral. It is postulated to be immune mediated leading to involvement and recruitment of T cells in skin, which can be demonstrated on immunohistochemical analysis. The mechanism of hypersensitivity is illustrated in Fig. 43.1.

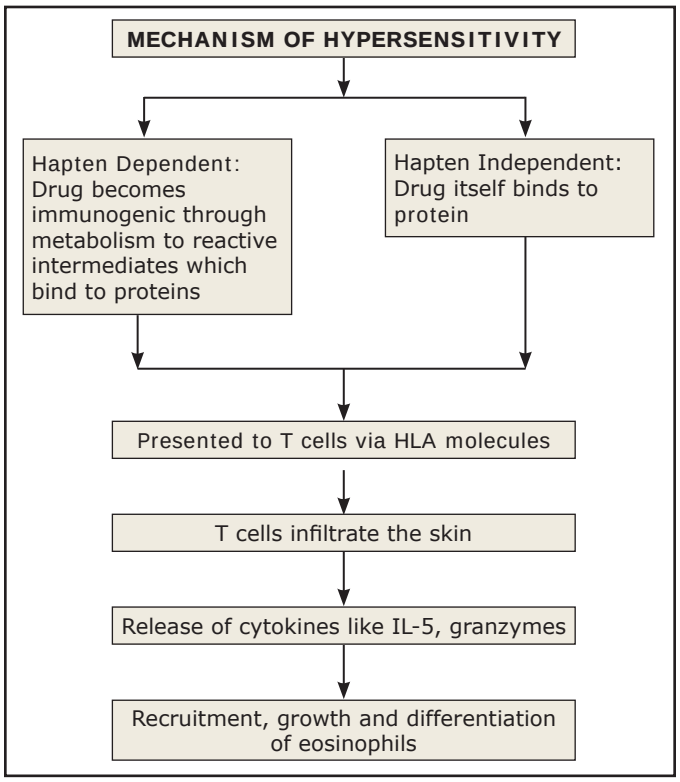

Fig. 43.1: Mechanism of hypersensitivity. IL, interleukin; HLA, human leukocyte antigen.

All NNRTI (nevirapine, efavirenz and delavirdine), NRTI (abacavir), and protease inhibitor (PI) (amprenavir) are part of common antiretroviral therapy (ART) that can cause hypersensitivity. It can be due to other drugs given to AIDS cases for treatment (antituberculosis drugs) as well as prophylaxis of opportunistic infections such as cotrimoxazole for *Pneumocystis Jiroveci* pneumonia.

Clinical Manifestations

Clinical features range from skin reactions to internal organ involvement.

Internal organ involvement may result in pericarditis, myocarditis, pneumonitis, pancreatitis, anicteric hepatitis and acute interstitial nephritis. It can also cause hypotension, drug-induced thrombocytopenia, anemia and neutropenia.

Skin reactions include Morbilliform/maculopapular rash, mucosal ulceration, urticaria, erythema multiforme, SJS/TEN, exfoliative dermatitis, hyperpigmentation, diffuse hair loss, nail changes etc. Some of the common cutaneous ADRs are described below.

COMMON CUTANEOUS REACTION PATTERNS

Maculopapular Eruptions (Morbilliform Rash)

They usually occur in patients on cART with or without antimicrobials such as sulfa group of drugs, penicillin, and cephalosporins. They are characterized by widespread, pruritic, confluent pink-to-red macules and papules usually on trunk and proximal extremities. They appear within 2–10 weeks of first exposure to the offending drug and may take up to 2 weeks to resolve after its discontinuation. Re-exposure to the offender, however, may trigger the reaction in as early as 1–2 days. Maculopapular rash may be of varied severity. Grade 1 includes mild (localized) rash, grade 2 (Fig. 43.2) includes moderate rash without any systemic or mucosal involvement, whereas grade 3 includes rash involving >50% of body surface area (Figs. 43.3 A and B) or having mucosal ulceration or systemic involvement, grade 4 includes SJS/TEN. Maculopapular reaction may progress to exfoliative dermatitis. Presence of ulcers and necrosis with mucosal involvement should alarm the clinician about the possibility of a bullous reaction.

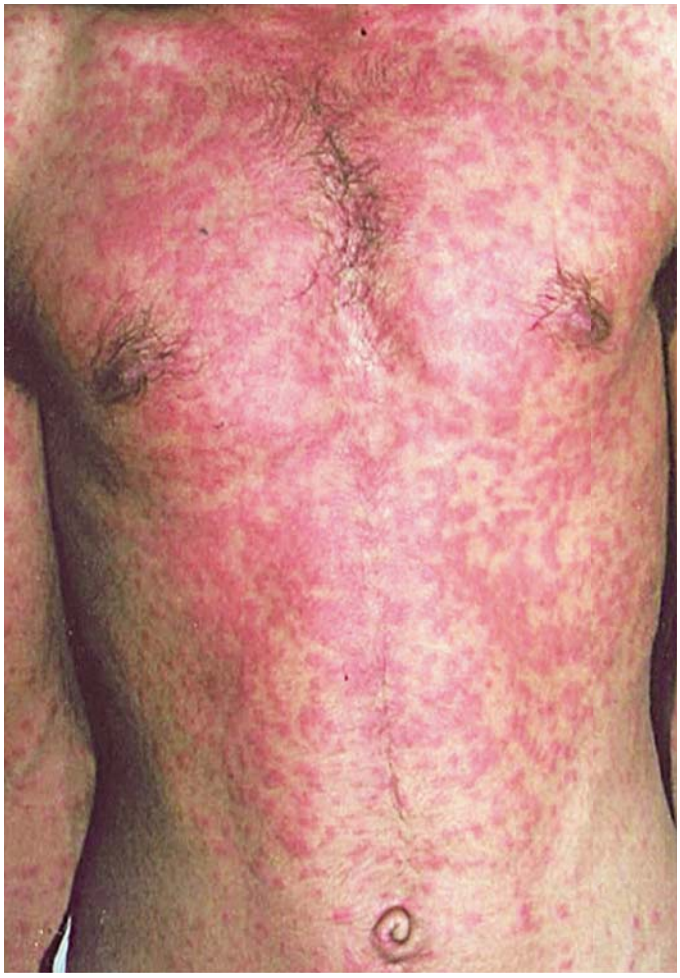

Fig. 43.2: Efavirenz-induced Maculopapular rash.

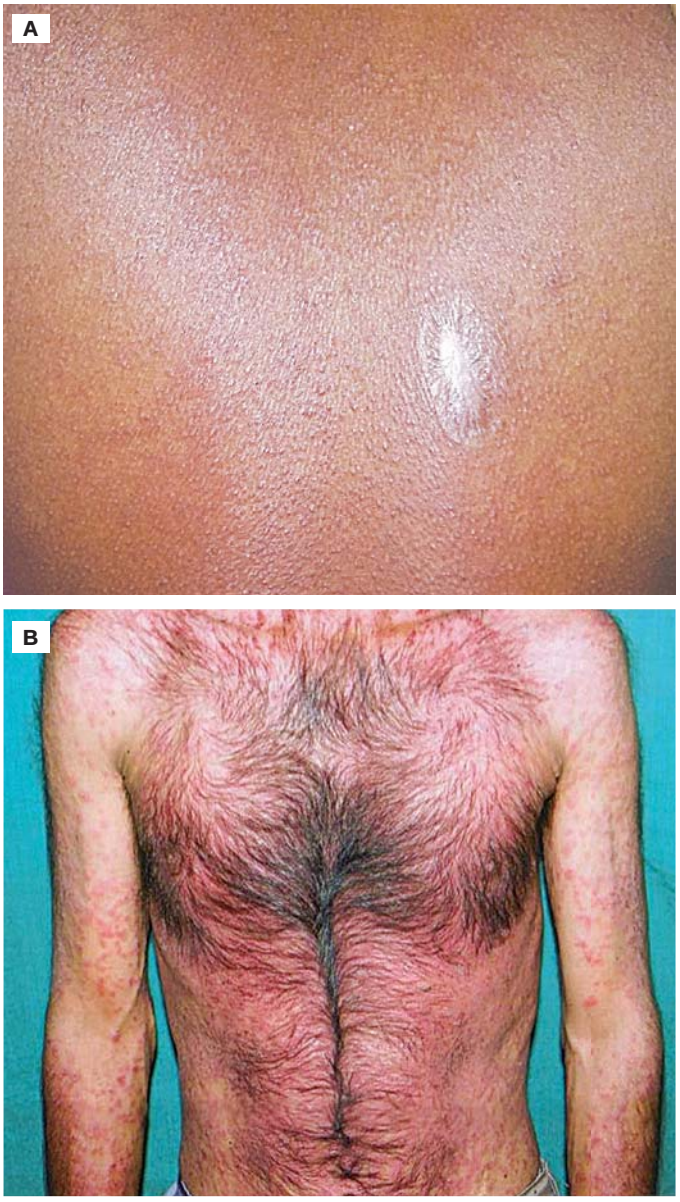

Fig. 43.3: (A & B) Nevirapine-induced Grade III rash.

Hyperpigmentation

Hyperpigmentation of the skin and nails (Fig. 43.4) has been observed in chronically HIV-infected cases and can be due to photosensitivity as well. It can occur due to cART also, but it is difficult to differentiate whether it is due to HIV or drug. Drug-induced nail pigmentation characteristically affects several nails, which reverses on discontinuation of the causative drug .

Urticaria

Drug-induced urticaria is usually acute and generalized and is most commonly mediated by IgE antibodies. It resolves on discontinuation of the drug and systemic antihistamines; however, severe cases may require corticosteroid administration.

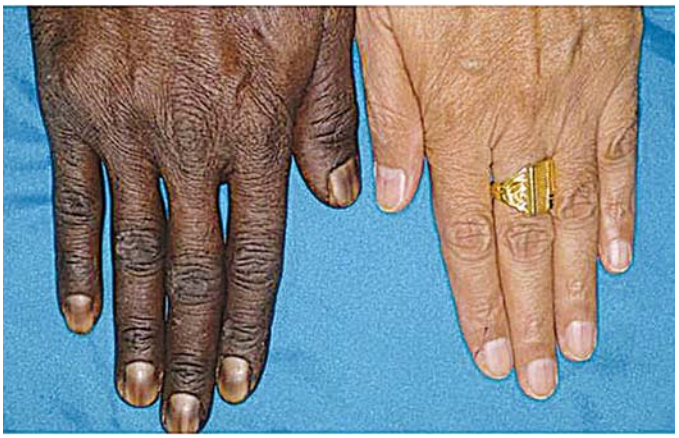

Fig. 43.4: Zidovudine-induced skin and nail hyperpigmentation. Author's hand is shown for comparison.

Stevens–Johnson Syndrome/Toxic Epidermal Necrolysis

SJS and TEN are rare severe cutaneous reactions caused by ART. They manifest as widespread skin lesions—targetoid or confluent, tender erythematous macules with blisters and mucosal involvement (Fig. 43.5) usually preceded by a prodrome of fever, nausea, vomiting, malaise, myalgia and arthralgia. Pseudo-Nikolsky's sign, i.e. detachment of epidermis by finger with lateral pressure, is positive. SJS involves <10% of the body surface area, whereas TEN >30% (Fig. 43.6) with the intermediate 10%–30% termed as an overlap syndrome. Histology shows full-thickness epidermal necrosis with minimal changes in underlying dermis. Widespread apoptosis of epidermal cells may be due to upregulation of FAS ligand on the keratinocyte membranes. Sequelae include pathological scarring, alteration in skin pigmentation, ocular diseases, heterotrophic ossification and abnormal nail growth.

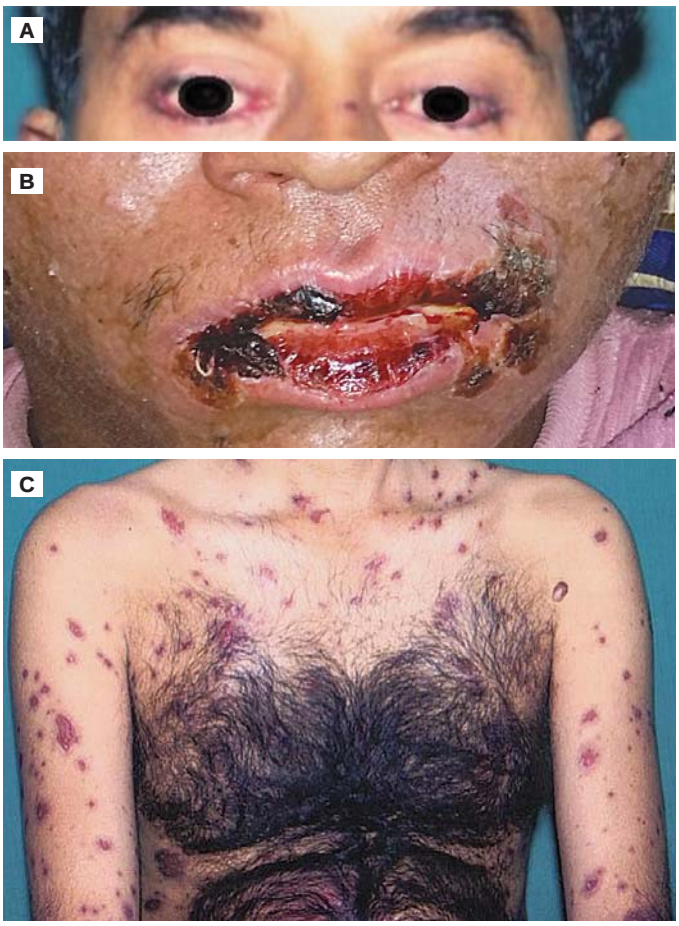

Fig. 43.5: Nevirapine-induced Stevens–Johnson syndrome showing mucosal involvement: (A) Ocular; (B) Oral; and (C) Involvement of trunk.

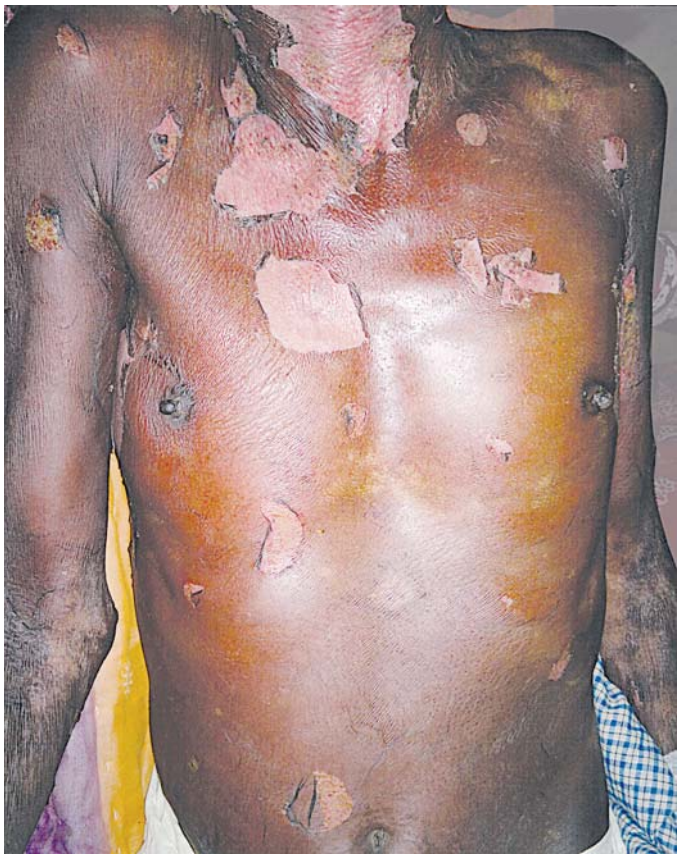

Fig. 43.6: Widespread necrolysis in a patient of AIDS on nevirapine.

Drugs implicated in erythema multiforme/SJS/TEN in HIV/AIDS cases include abacavir, nevirapine, efavirenz, co-trimoxazole, isoniazid, phenytoin, carbamazepine, clarithromycin, fluconazole, griseofulvin, vancomycin, etc.

Lipodystrophy

Overall prevalence of lipodystrophy was found to be about 50% after 12–18 months of therapy. Clinical features include peripheral fat loss (loss of buccal fat and thinning of extremities and buttocks) and central fat accumulation over abdomen (Crix belly), breasts (gynecomastia), and dorsocervical spine

(buffalo hump). Lipodystrophy is most commonly seen with the use of PIs. One should always rule out any recent severe illness associated with weight loss.

Drug Hypersensitivity Syndrome (DHS)

Also known as DRESS (drug rash with eosinophilia and systemic symptoms), it is usually manifested within 1–6 weeks of initiation of drug therapy, classically abacavir. It is characterized by dusky reddish, pruritic, confluent rash that may desquamate and lead to exfoliative dermatitis, facial edema (hallmark), fever, and fatal complications such as pneumonitis, nephritis and hepatitis.

Retinoid-like Effects

Indinavir monotherapy is known to cause xerosis (14%) and dry mouth (9%), while in combination it can cause hair loss, ingrown toe nails and paronychia.[8]

DIFFERENT CLASS OF ARTs AND CADRs CAUSED

CADRs due to NRTIs

Abacavir can cause hypersensitivity in 2%–9%[9] of cases due to immunological and genetic factors. It can be diagnosed on the basis of following clinical criteria: Fever, rash, nausea, vomiting, headache, lethargy, myalgia, arthralgia, or gastrointestinal symptoms, occurring within 6 weeks after the commencement and resolving within 72 hours of withdrawal of the drug. Zidovudine is reported to cause nail pigmentation. The common ADR observed with stavudine is disfiguring lipoatrophy (Fig. 43.7). Among NRTIs, least ADRs are reported with lamivudine. Emtricitabine can cause asymptomatic rash (usually grade 1) on palms and soles in 1.5% cases. Didanosine, tenofovir, and zidovudine can cause allergic reaction in the form of rash.

CADRs due to NNRTIs

NNRTI as a group is the commonest cause of CADR. In a casualty assessment–based study carried out at Zimbabwe, of total 221 AIDS cases on ART, 13.1% cases developed CADRs, of which 72.4% were due to NNRTIs (nevirapine and efavirenz) and remaining 27.6% cases due to other drugs.[10] NNRTIs cause erythematous, widespread, maculopapular rash in 10%–17%[11] cases with approximately 8%–12% cases experiencing severe rash with discontinuation in about 2%–10% cases.[12–14]

Nevirapine may cause rash in 17%–32% cases, its incidence being 2–8 times higher in Thai adults than Asian adults.[13]

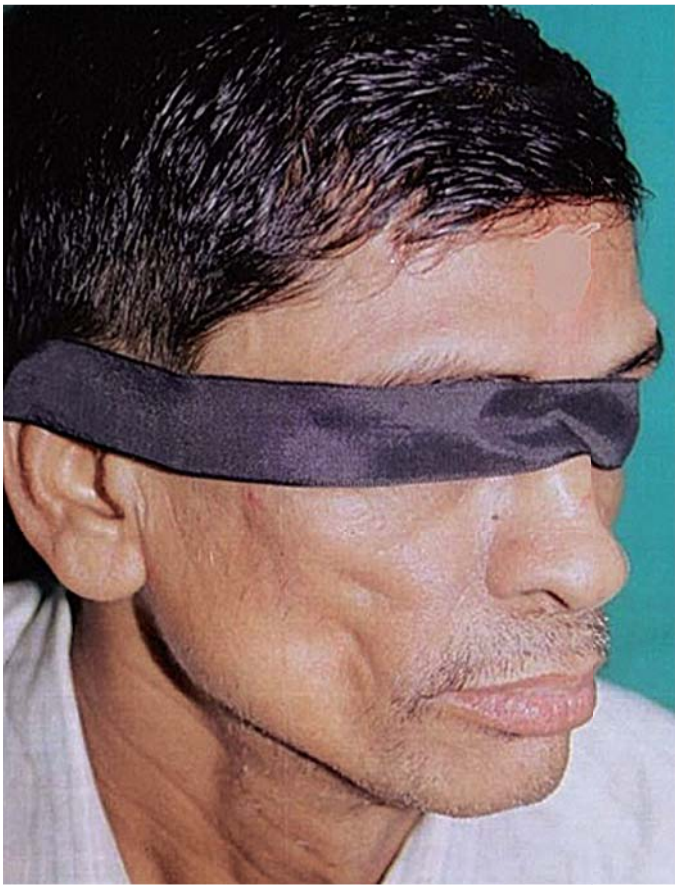

Fig. 43.7: Stavudine-induced lipoatrophy.

Efavirenz may cause grade 1 or 2 rash or even fatal reactions such as SJS or TEN in about 0.1% cases compared to 0.3%–1% cases with nevirapine.[15]

Etravirine-induced skin rash, most common during the second week of therapy, has led to its discontinuation in about 2% cases,[16] more frequently in women.[17]

CADRs due to PIs

Lopinavir, atazanavir, and fosamprenavir may cause skin rash in 2%–4%[18], 6%[19] and 19%[20,21] cases, respectively, with discontinuation rate being less than 1%.

CADRs due to Entry Inhibitors, Fusion Inhibitors, and CCR5 Inhibitors

Enfuvirtide hypersensitivity is rare with <1% cases showing systemic manifestations such as fever and hepatitis along with rash occurring 1 week after initiation.[22] Maraviroc hypersensitivity is rare and is usually seen in patients with impaired liver function.

The different types of CADRs to various antiretroviral agents are summarized in Table 43.1.[23]

Table 43.1: ADR due to ART

ART	Cutaneous adverse reactions	Other adverse effects
All NRTIs	1. Pruritus 2. Exanthema 3. Urticaria	Nausea, vomiting, lactic acidosis, pancreatitis, bone marrow suppression, arthralgia, myalgia, dyspnea
Zidovudine	1. Nail hyperpigmentation 2. Mucocutaneous hyperpigmentation 3. Hypertrichosis 4. Eyelash hypertrichosis 5. Hypersensitivity syndrome 6. Leukocytoclastic vasculitis 7. Heightened reaction to mosquito bites 8. Paronychia with lateral nail-fold pyogenic granuloma–like lesions 9. Lipodystrophy	Myopathy
Lamivudine	1. Allergic contact dermatitis 2. Vasculitis 3. Anaphylaxis 4. Angioedema 5. Gynecomastia 6. Lipodystrophy 7. Diaphoresis 8. TEN	Peripheral neuropathy
Stavudine	1. Lipoatrophy 2. Gynecomastia 3. Neutrophilic eccrine Hidradenitis 4. Tendon xanthomas 5. Diaphoresis	Peripheral neuropathy
Emtricitabine	1. Hyperpigmentation	Nausea, headache, bad dreams, fatigue
Tenofovir	1. Toxic erythema 2. Diaphoresis	Fanconi syndrome, osteoporosis, osteomalacia
Abacavir	1. Hypersensitivity (HLA-B57*01) 2. SJS/TEN 3. Kawasaki syndrome 4. Anaphylaxis 5. Lipodystrophy	Lymphopenia, leukopenia, thrombocytopenia, elevated transaminase levels
Didanosine	1. Leukocytoclastic vasculitis 2. SJS 3. Papuloerythroderma of Ofuji 4. Alopecia 5. Gynecomastia 6. Acral erythema 7. Diaphoresis	Dysgeusia, xerostomia, gout, acute gouty arthritis

(Continued..)

Table 43.1: ADR due to ART (Continued)

ART	Cutaneous adverse reactions	Other adverse effects
Zalcitabine	1. Hypersensitivity syndrome 2. Photosensitivity 3. Acne 4. Granuloma annulare 5. Bullous eruption 6. Diaphoresis	Peripheral neuropathy
All NNRTIs	1. Pruritus 2. Exanthems 3. SJS/TEN	Headache, nausea, vomiting, vivid dreams, hepatitis, osteonecrosis
Nevirapine	1. Morbilliform eruption 2. SJS 3. TEN 4. DRESS	Hepatotoxicity
Efavirenz	1. Morbilliform eruption 2. Mucosal ulceration 3. Photosensitivity 4. DRESS syndrome 5. Leukocytoclastic vasculitis 6. Seborrhea 7. Eczema 8. Annular erythema 9. Flushing 10. Folliculitis	Lymphopenia, leukopenia, thrombocytopenia, insomnia, nightmares, hyperlipidemia
Etravirine	1. Morbilliform eruption 2. SJS 3. Gynecomastia 4. Hyperhidrosis 5. Lipohypertrophy	Peripheral neuropathy, hepatitis
Rilpivirine	1. Cushingoid features	QT interval prolongation
Protease inhibitors	1. Lipodystrophy 2. Hypersensitivity reaction 3. Acute generalized exanthematous pustulosis 4. Xerosis 5. Tendon xanthomas 6. Acanthosis nigricans 7. Lipomatosis	Insulin resistance, hyperglycemia, hyperlipidemia, anorexia, hepatotoxicity, rhabdomyolysis, osteonecrosis, dysgeusia, neurotoxicity, blood dyscrasias
Ritonavir	1. IgA-mediated hypersensitivity reaction 2. Drug reaction 3. Hematoma formation 4. Hair loss 5. Acne 6. Seborrhea 7. Ecchymosis 8. Paresthesia	Dysgeusia, perioral paraesthesia, epilepsy, thrombophlebitis

(Continued..)

Table 43.1: ADR due to ART (Continued)

ART	Cutaneous adverse reactions	Other adverse effects
Nelfinavir	1. Morbilliform eruption 2. Generalized urticaria 3. Lichenoid reaction 4. Palmar erythema 5. Vasculitis	–
Darunavir	1. Erythema multiforme 2. SJS 3. Hyperhidrosis	–
Atazanavir	1. Morbilliform eruption 2. Hair and nail changes 3. Photosensitivity 4. Eczema 5. Vesiculobullous eruption 6. Gynecomastia 7. Diaphoresis	Hyperbilirubinemia
Tipranavir	1. Photosensitivity	Dyspnea
Amprenavir	1. Toxic erythema	–
Fusion inhibitor Enfuvirtide	1. Injection site reaction—erythema, induration, discomfort, pruritus, pain 2. Xerosis 3. Acne 4. Papillomas 5. Herpes simplex 6. Paraesthesia	Depression, myotoxicity
Integrase inhibitors Raltegravir	1. Diaphoresis 2. Pruritus 3. Hypersensitivity 4. Morbilliform eruption	Insomnia, dizziness, hepatitis, nausea, diarrhea, headache
CCR5 Inhibitors Maraviroc	1. Pruritus 2. Allergic reaction 3. Lipodystrophy 4. Folliculitis	Vascular hypertensive disorder, nausea, diarrhea, abdominal pain, stomatitis, myotoxicity, upper respiratory tract infections, sleep disturbance

SJS/TEN - Stevens–Johnson syndrome/toxic epidermal necrolysis; DRESS - drug rash with eosinophilia and systemic symptom; ART - antiretroviral therapy; NRTI - nucleoside reverse transcriptase inhibitors; NNRTI - non-nucleoside reverse transcriptase inhibitors.

Source: Bunker and Piguet. [23]

REACTIONS TO COADMINISTERED DRUGS

Prophylactic Drugs

Co-trimoxazole (trimethoprim/sulfamethoxazole) is used in the prevention of *Pneumocystis Jiroveci* pneumonia. It may be associated with allergic reactions manifesting as urticaria, exanthematous rash, eczematous reactions, fixed drug eruptions, erythema multiforme, SJS and TEN etc. Such reactions occur more commonly in HIV/AIDS cases (60%) compared to HIV-negative cases (5%). Risk Factors include male sex, history of syphilis, lower CD4 count, higher CD4:CD8, and a higher total plasma protein concentration. Isoniazid also can lead to hypersensitivity rash.

Drugs to Treat Opportunistic Infections

Antituberculosis Drugs

Rash and/or fever are most common adverse reactions seen with rifampicin followed by pyrazinamide, isoniazid, ethambutol and streptomycin. The most common manifestation includes maculopapular rash, urticaria, angioedema, erythroderma, SJS and TEN.

Anti-toxoplasmosis Drugs

Hypersensitivity has been noted with the use of pyrimethamine–sulfadoxine and clindamycin in the form of generalized maculopapular pruritic reaction, angioedema, DRESS, SJS and TEN.

Antifungal Drugs

Fluconazole used in candidiasis, cryptococcosis, aspergillosis, histoplasmosis, etc. has been reported to cause maculopapular rash, fixed drug eruptions, diffuse erythema, angioedema, rash with acute hepatitis and SJS.

DIAGNOSIS

Precise diagnostic tool for confirming the suspected drug is not available. Causality assessment through a standardized WHO scoring system or with the help of Naranjo's scale is useful. Rechallenge is better avoided if there is mucosal involvement or grade III/IV rash. Role of patch testing is studied for confirming suspected abacavir hypersensitivity, but the predictive value of patch testing is not certain. Lymphocyte transformation tests have been used but it is more of a research tool.

MANAGEMENT

In 50% of cases with isolated mild-to-moderate skin rash, spontaneous resolution without discontinuation of therapy is observed. Drugs need to be stopped if there is mucosal involvement, blistering, exfoliation, and/or elevation of transaminases more than five times the upper limit with symptoms like jaundice, upper abdominal pain (tender hepatomegaly), fever >39°C, or intolerable pruritus. Standardized causality assessment helps in identifying a causative agent with greater accuracy.

Symptomatic treatment with antipyretics and antihistamines are commonly used. In SJS and TEN, maintenance of fluid and electrolyte balance, nutritional support, and systemic treatment to stop the progression of skin disease is carried out. In early stages of TEN, short courses of systemic corticosteroid have been proposed, but its efficacy is not supported by controlled trial. Early treatment with intravenous immunoglobulin at a total dose of 3 g/kg over 3 consecutive days is reported to be beneficial. However, potential deterioration due to intravenous immunoglobulin administration in elderly patients and patients with impaired renal function has been reported. Corticosteroids instituted within first 24 hours of co-trimoxazole hypersensitivity have been reported to be beneficial.

DESENSITIZATION

Desensitization has been used with some success to reinitiate the drug in patients who have experienced an allergic reaction with zidovudine and enfuvirtide. However, desensitization with abacavir is an absolute contraindication.

CROSS-REACTIVITY

The rate of NNRTI cross-reactivity is not known. Switching from nevirapine to efavirenz and vice versa due to skin rashes was associated with recurrence of severe rash as reported in a small case study and monitoring of switch to alternate NNRTI is necessary.

PRETREATMENT SCREENING

Hypersensitivity associated with nevirapine is more likely to occur at higher CD4 counts. Screening for HLA-B*5701 should be carried out before starting abacavir. Meticulous personal and family history of drug reaction is essential.

To minimize adverse drug reactions, start with different groups of drugs with minimal overlapping toxicities.[24] Different clinical scenarios such as coexisting viral and bacterial infections with concomitant treatment, pregnancy and lactation, and age need to be considered.

CONCLUSION

Skin bears the brunt of commonly occurring ADRs due to cART. Early identification and prompt withdrawal of drug in severe reactions are of paramount importance. Symptomatic and supportive therapy is the key to manage ADR. Awareness on the part of treating physician and education of health-care worker and patient can facilitate early recognition of ADR. ADR monitoring and ascertaining causality in resource-limited settings remain crucial challenges. A Zimbabwe-based pharmacovigilance study shows that discrepancy exists between the subjectively reported CADRs by the physician and the data obtained through objective scoring.[10] This necessitates standardized causality assessment by Naranjo's ADR probability score or WHO-Uppsala Monitoring Center scoring system. Further research is needed in direction of identifying predisposing factors, confirmation of drug responsible for ADR and in the development of predictive biomarkers for drug hypersensitivity.

LEARNING ESSENTIALS

- Cutaneous ADRs are frequently seen in HIV/AIDS due to various factors like altered drug metabolism, immune dysregulation, genetic predisposition, polypharmacy, oxidative stress etc.
- To avoid over diagnosis by physician, appropriate causality assessment should be done to establish a relationship between ADR and suspected drug.
- Among ART, NNRTI is the most common group causing CADR.
- Abacavir hypersensitivity has been linked with HLA-B*5701, hence screening before starting the therapy is essential.
- Drug can be continued even after grade I/II skin rash without any systemic or mucosal involvement. However, grade III/IV rash with constitutional symptoms or laboratory abnormalities may necessitate discontinuation of drug.
- Supportive and specific systemic treatment may be instituted when required. Short course of corticosteroids is helpful in generalized body rash. Early institution of corticosteroids in SJS/TEN has been considered to be beneficial.
- ADR reporting to the Pharmacovigilance Programme of Government of India should be done by the treating physician (www.ipv.gov.in/PvPI).

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Chapter

44

Cutaneous Adverse Drug Reactions in Children

Sandipan Dhar • Sahana M. Srinivas

SUMMARY

- Cutaneous adverse drug reactions are the most common type of drug reactions seen in children.
- Maculopapular rash and urticarial eruptions are the most common clinical or morphological patterns seen in children.
- Exanthematous drug eruptions should be differentiated from viral exanthem in children.
- Most of the cutaneous drug reactions in children are non serious and require only symptomatic treatment.

INTRODUCTION

Cutaneous adverse drug reactions (CADRs) are the most common type of drug reactions seen in children. There is growing awareness about the importance of cutaneous manifestations of drug reaction in children, which is well documented in several studies. Majority of these reactions are not serious, but they pose a diagnostic challenge as they mimic various childhood exanthem. Viral exanthem is the most common differential diagnosis of drug reaction in children. A systematic approach is necessary to diagnose drug reaction so as to prevent the child from getting exposed to noxious drug reactions.[1] A good clinical knowledge and vigilance about the predisposing factors, clinical pattern and monitoring guidelines can prevent further exposures.

EPIDEMIOLOGY

The exact incidence of CADRs is not known as it varies in different studies. Many of the CADRs are not recognized and hence go underreported. There are no adequate controlled clinical trials on drug reactions in children. The frequency and clinical pattern of drug reactions depend on the pharmacogenetic traits of a population. Meta-analysis of prospective studies showed that the overall incidence of adverse drug reactions (ADRs) in hospitalized children was 9.53% and was 1.5%–2.5% in outpatient setting.[2,3] The World Health Organization's (WHO) ADR VigiBase® data showed the CADRs accounted for 35% of all suspected ADRs in children and the majority of the reported reactions were due to anti-infective, neurology and dermatology medications.[4] Kushwaha et al. in their study reported CADR as the most common type of reaction accounting for 67.12% of ADRs in hospitalized children.[5] Among the pediatric age group, mortalities due to ADRs were reported more between the age group of newborn and 2 years.[6] In a large prospective study of ADRs of 24,000 ambulatory pediatric patients over a period of 1 year showed CADRs (36%) to be the most common type of ADRs.[7] In another large outpatient setting study that comprised review of 6000 medical records of children treated with antibiotics, 7.3% developed skin rash after prescribing antibiotic, which included penicillins, sulfonamides, and cephalosporins.[8]

Majority of the CADRs in children are not serious, although previous studies have documented 2% of the cases being severe and life-threatening.[9] In a recent study published by the Canadian society, 16% cases of ADRs were reported to be cutaneous, with 66% of them being serious in nature; of these most of the reactions were due to antimicrobials and antiepileptics.[8] Asian studies have shown younger age group being affected more than older age group as compared to European and American studies. Several studies have shown maculopapular eruption to be the most common clinical pattern of CADRs in children.[10,11]

ETIOPATHOGENESIS (SPECIFIC ISSUES IN CHILDREN)

The pharmacokinetics and pharmacodynamics vary

among adults and children. Drug reactions occur due to immunological and non-immunological mechanism. The frequency of drug rash is low in younger age group, probably due to less cumulative drug exposure, rapid dissipation of immunoglobulin E (IgE), and poorly developed immunopathological mechanism, especially in neonates such as impaired T-cell reactivation, diminished production of lymphokines, decreased chemotactic activity of macrophages, and less functional competence of natural killer cells.[11,12] Risk factors associated with ADRs in children include pharmacogenetic variation; deficient drug-metabolizing enzymes; human leukocyte antigen (HLA) association with severe cutaneous adverse reactions (SCARs), polypharmacy, off-label use of drugs, drug interaction, active viral infection (HHV-6) and renal insufficiency.[1,2] Recurrence of drug hypersensitivity syndrome (DHS) is associated with reactivation of HHV-6.

CLASSIFICATION

There are more than 25 different patterns of CADRs described in literature.[13] CADRs may be mild, localized to limited area of skin and mucosae, or severe (SCARs) where the reaction is generalized along with systemic involvement. There is significant mortality and morbidity associated with SCARs. Different clinical reactions based on severity are summarized in Table 44.1. On the basis of the morphological pattern, CADRs can be exanthematous, urticarial, bullous and pustular (Table 44.2).

Table 44.1: Types of CADRs based on severity

Nonsevere reactions	Severe reactions (SCARs)
• Maculopapular rash (exanthematous eruption) • Urticaria • Fixed drug eruption • Acneiform eruption • Erythema multiforme	• Angioedema • SJS/TEN • Drug hypersensitivity syndrome • Drug-induced anaphylaxis • SSLR • AGEP • Drug-induced erythroderma

SCAR - severe cutaneous adverse reaction; SJS - Steven–Johnson syndrome; TEN - toxic epidermal necrolysis; SSLR - serum sickness–like reaction; AGEP - acute generalized exanthematous pustulosis.

Table 44.2: Different morphological pattern of drug reactions with most common causative drugs

Clinical morphology	Types	Common causative drugs
Exanthematous	Simple eruptions	Penicillin, sulfonamides, amoxicillin, antiepileptics
	Hypersensitivity syndromes	Phenytoin, phenobarbitone, carbamazepine, dapsone, allopurinol, antibiotics, lamotrigine
Urticarial	Urticaria/angioedema	Penicillin, NSAIDs, cephalosporins, sulfonamides, ACE inhibitors
	SSLR	Cefaclor, cefprozil, minocycline, infliximab, rituximab
Pustular	Acneiform eruptions	Corticosteroids, iodides, isoniazid, androgens, lithium, phenytoin
	AGEP	β-lactam antibiotics, macrolides
Bullous eruptions	Bullous FDE	Phenolphthalein, NSAIDs, sulfonamides, tetracyclines, lamotrigine
	EM/SJS/TEN	Anticonvulsants, sulfonamides, antibiotics, NSAIDs, dapsone
	Pseudoporphyria	Tetracyclines, furosemide, naproxen
	Pemphigus/BP/LAD	Penicillamine, captopril, penicillin, rifampin, vancomycin, diclofenac, piroxicam
Miscellaneous	NEH, FDE, drug-induced lupus, photosensitivity reactions, lichenoid eruptions, cutaneous pseudolymphoma, drug-induced vasculitis, pigmentary changes, nonscarring alopecia, psoriasiform reactions, pruritus, peripheral neuropathy, hair and nail changes, eruptions from biological therapies, anticoagulant-induced skin necrosis	Procainamide, hydralazine, isoniazid, minocycline, phenytoin, penicillin, sulfonamides, chloramphenicol, dopamine, mannitol, sodium bicarbonate, warfarin, antineoplastic drugs, antiretroviral drugs

SSLR - serum sickness–like reaction; AGEP - acute generalized exanthematous pustulosis; FDE - fixed drug eruption; EM - erythema multiforme; SJS - Stevens–Johnson syndrome; TEN - toxic epidermal necrolysis; BP - bullous pemphigoid; LAD - linear IgA disease; NEH - neutrophilic eccrine hidradenitis; NSAIDs - nonsteroidal anti-inflammatory drugs; ACE - angiotensin-converting enzyme.

CLINICAL FEATURES

Exanthematous Eruptions

Exanthematous eruptions (maculopapular/morbilliform/scarlatiniform) are the most common clinical patterns of CADRs in children and are well documented in various studies accounting to 95% of cases. In a study by Khaled et al., maculopapular eruption was seen in 57.7% of children, especially to antibiotics (80.7%).[14] In a study of clinical pattern in children and adolescents conducted in North India, the most common pattern was maculopapular eruptions.[11] Majority of the reactions occur during the first 2 weeks of exposure. In some children, reactions can develop after many years of having used the same drugs. Clinically manifest as widespread erythematous macules and papules that usually occur on trunk and later spread peripherally and become confluent (Fig. 44.1). Pruritus is a common feature of CADRs. Eruption resolves within 7–14 days with desquamation.[13] Most common drugs implicated are penicillin, sulfonamides and antiepileptics. Ampicillin-induced morbilliform eruption occurs in patients with active Epstein–Barr virus (EBV) infection.[15]

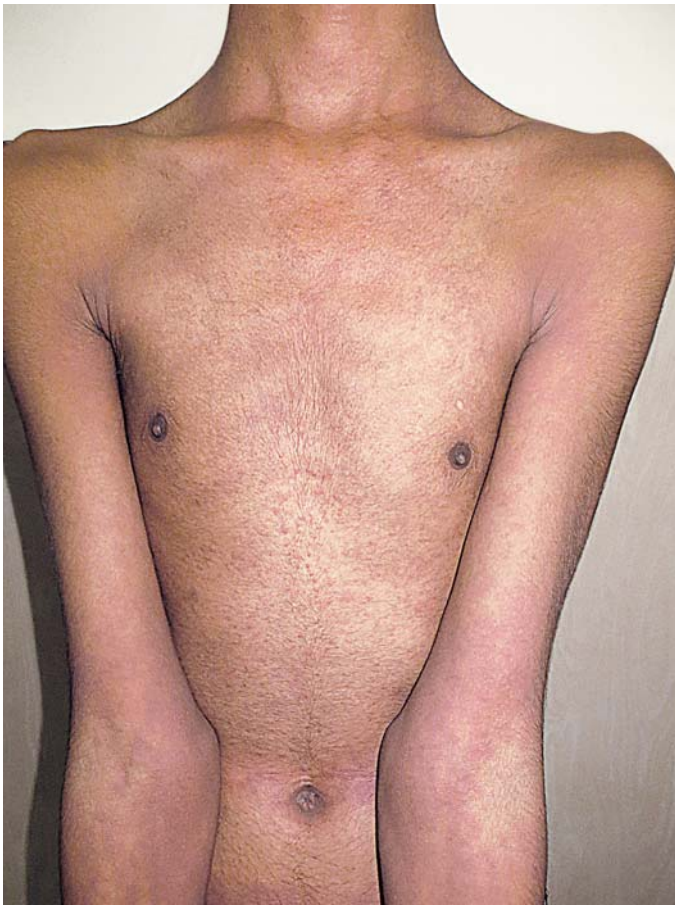

Fig. 44.1: Diffuse maculopapular eruption on trunk and upper limbs caused by amoxicillin.

In exanthematous eruption associated with fever with multiorgan involvement such as hepatitis, nephritis, pneumonia, vasculitis, meningitis and pharyngitis with lymph node involvement, DHS must be considered (Fig. 44.2). It is also known as drug reaction with eosinophilia and systemic symptoms (DRESS). DHS occurs in 1:3000 exposures and most frequently is associated with first exposure. Reaction is seen from 1 to 6 weeks after exposure.[16] The most common cause is aromatic anticonvulsant (Table 44.2). Cross-reactions can occur between all aromatic anticonvulsants such as phenytoin, phenobarbitone, carbamazepine and lamotrigine and this cross-reactivity is around 70%.[17] There is a familial occurrence of hypersensitivity to anticonvulsants with an autosomal recessive pattern of inheritance.[18] Recurrences can occur but are milder in nature. Mortality rate is around 8%–10%.

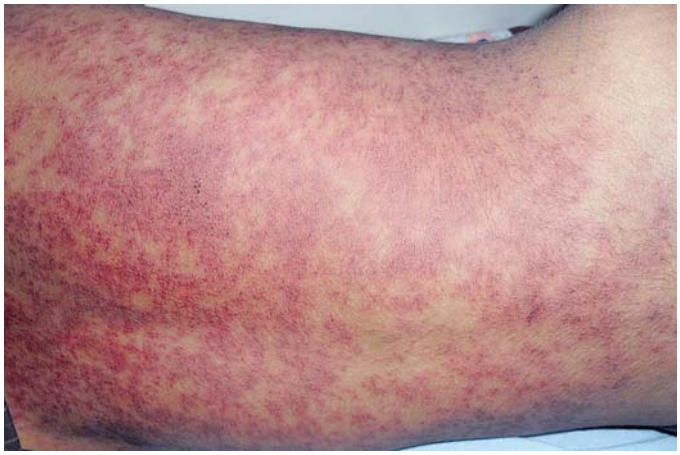

Fig. 44.2: Drug hypersensitivity syndrome with exanthematous eruption on trunk.

Urticarial Eruption

Several studies have shown that drug-induced urticaria comprises around 5%–15% of all CADRs in children making it the second most common CADR in children.[11,13,14] In a multicentric study of CADRs in children, the most frequent cutaneous reaction pattern was urticaria/angioedema (51.6%).[19] Urticaria is characterized by pruritic wheals that are transient and last up to 24 hours (Fig. 44.3). Angioedema is nonpruritic and lasts for 1–2 hours and mainly involves eyes, lips and other mucous membranes. Angioedema is most commonly caused by angiotensin-converting enzyme (ACE) inhibitors. Giant urticaria is a distinctive type of urticaria seen in children between 1 and 5 years, which is caused by antibiotics and antipyretics. It is characterized by annular, arcuate and polycyclic wheal (Fig. 44.4).[20] It should be differentiated from serum sickness–like reaction (SSLR) and erythema multiforme (EM). SSLR presents with skin rash (urticaria or EM), periocular

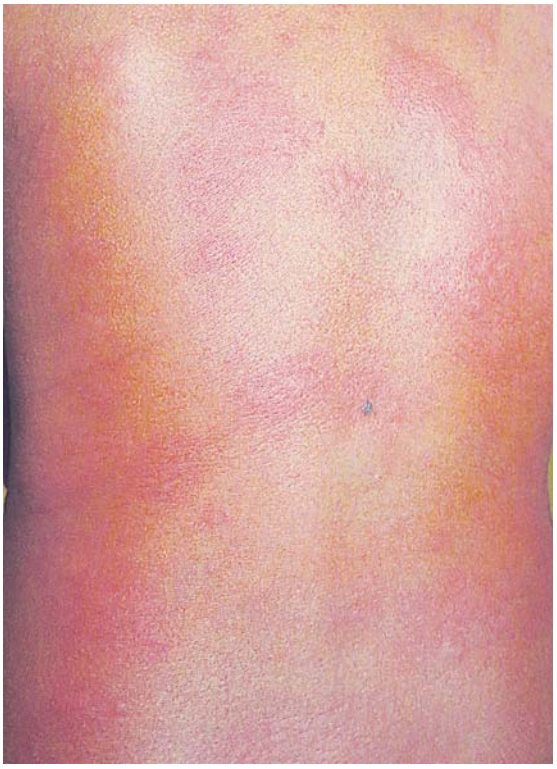

Fig. 44.3: Wheals present in urticarial eruption.

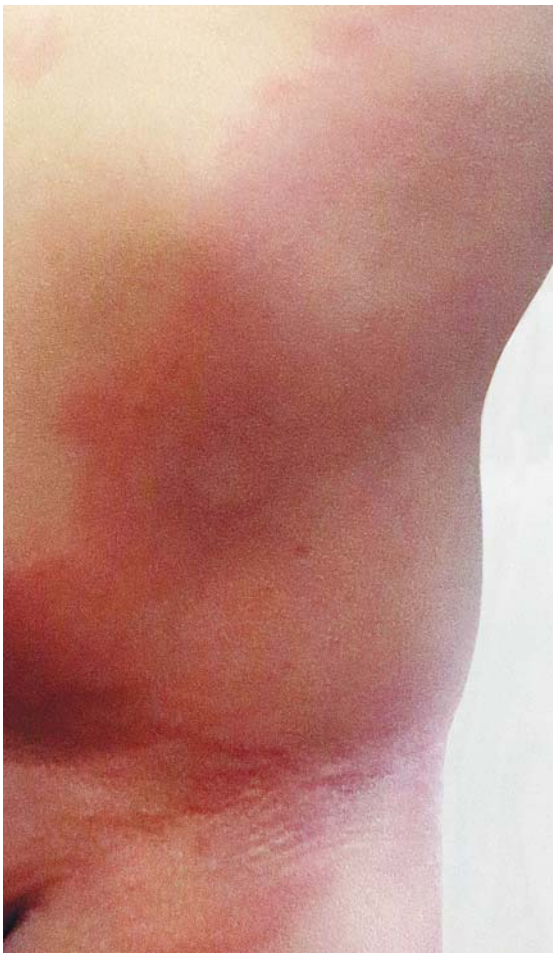

Fig. 44.4: Giant urticaria in a 3-year-old child caused by amoxicillin.

edema, fever, arthralgia, lymphadenopathy, and eosinophilia and is seen within 1–3 weeks of exposure to the causative drug. SSLR is seen most commonly with cefaclor with a risk of 0.024%–2.6%.[21]

Pustular Eruptions

Drug-induced acne occurring on trunk, and extremities are usually monomorphic. In children, they are seen commonly with systemic corticosteroids and antitubercular drugs. Acute generalized exanthematous pustulosis (AGEP) though common in adults, only a few cases have been reported in children. It presents as nonfollicular sterile pustules on an edematous, erythematous base along with fever, and leukocytosis. In children, AGEP is attributed to antibiotics, antipyretics, analgesics, and vaccines.[22] It resolves by 7–10 days with generalized desquamation.

Bullous Eruptions

There are a lot of controversies till date whether EM, Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are part of a spectrum or represent different entities. All these reaction patterns present with atypical skin lesions, mucous membrane involvement and epidermal necrosis with skin detachment. EM minor (classical EM) is characterized by typical target lesions with three zones. Atypical target lesions with flat macules with or without blisters may be present. On the basis of the body surface area (BSA), epidermal detachment less than 10% defines SJS and more than 30% defines TEN (Figs. 44.5, 44.6, and 44.7). There may be an overlap of SJS and TEN

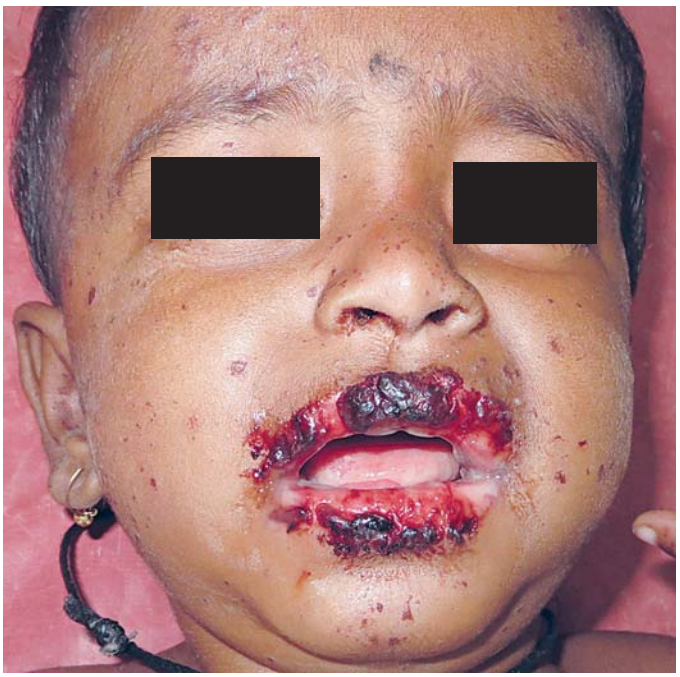

Fig. 44.5: Steven–Johnson syndrome with mucosal involvement.

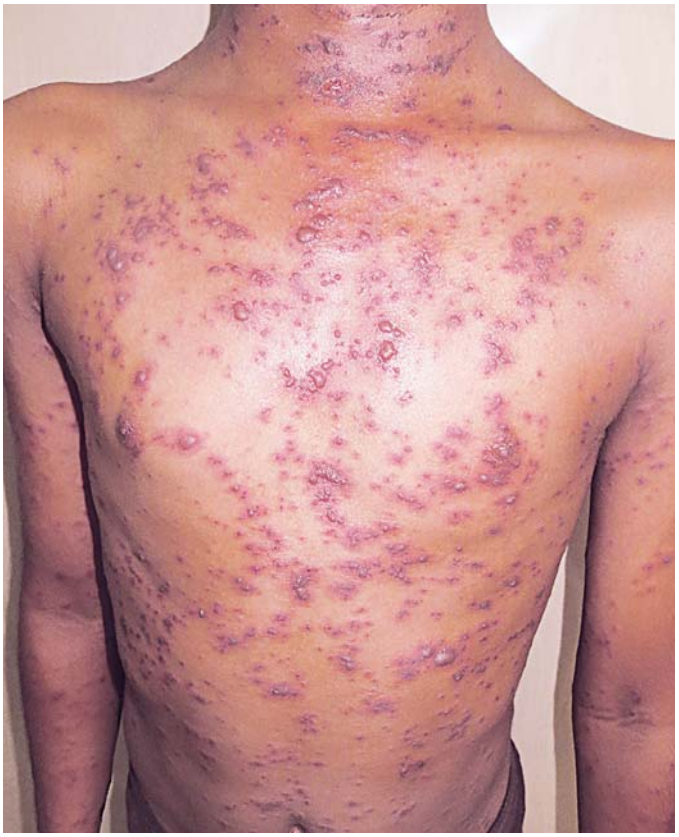

Fig. 44.6: Multiple blisters on trunk in Steven–Johnson syndrome.

involving 10%–30%.[23,24] SJS involves two mucosal sites that usually precedes the onset of skin lesions by 1–2 days. Drugs have been implicated as the causative factor in 50% of pediatric patients in SJS.[25] TEN presents initially as ill-defined erythematous macule with purpuric centers and progresses to cause extensive epidermal detachment (Fig. 44.7). Mucous membrane involvement is less in TEN.

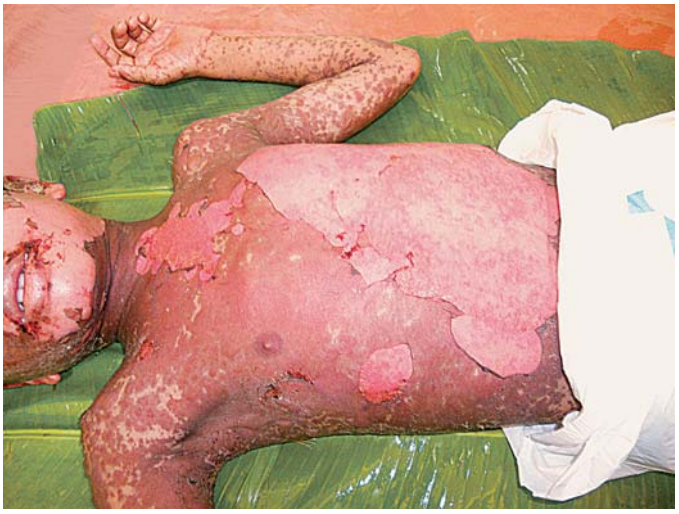

Fig. 44.7: Toxic epidermal necrolysis (TEN) showing epidermal detachment.

Mortality is more in TEN. Complications associated with TEN are listed in Table 44.3. The severity and prognosis of TEN is based on SCORTEN scale.[26]

Table 44.3: Complications with toxic epidermal necrolysis

Acute complications	Chronic complications
• Hypovolemia • Dehydration • Pneumonia • ARDS • Anemia/leukopenia • Esophageal erosions • GI hemorrhage • DIC • Septicemia	• Corneal scarring • Esophageal strictures • Phimosis • Pigmentary changes • Nail dystrophy • Contractures • Melanocytic nevi

ARDS - acute respiratory distress syndrome; GI - gastrointestinal; DIC - disseminated intravascular coagulation.

Fixed Drug Eruption

Fixed drug eruption (FDE) is characterized by lesions that occur at the same sites, whenever the offending drug is ingested. It presents as well-defined, round-to-oval, edematous dusky-brown macule or bullae. Sites commonly involved are genitalia, perianal area, lips, hands, and feet (Figs. 44.8 A and B). More than 100 drugs have been implicated in causing FDE. It develops 30 minutes to 16 hours after ingestion of medication.[27,28] In one study, trimethoprim/sulfamethoxazole was the causative drug in 50% children.[29]

Miscellaneous Pattern of Drug Reaction in Children

Some of the rare reaction patterns seen in children are depicted in Table 44.2. Pseudoporphyria is a rare type of drug-induced blistering eruption presenting as vesicles and bullae on photodistributed areas. Naproxen is the most frequent cause of pseudoporphyria frequently prescribed for rheumatological disorders in children.[30] Propranolol, a widely used drug to treat infantile hemangioma in children, causes acrocyanosis and this has been reported in several cases.[31] Acral erythema is a rare reaction pattern seen in children taking high dose of chemotherapy. Methotrexate-induced acral erythema has been reported in children.[32] There is a prodrome of burning, dysesthesia, and later progression to blisters, fissuring and desquamation. Drug-induced lupus and vasculitis are rarely seen in children. Anticoagulants-induced reactions include skin necrosis and rarely life-threatening reaction.

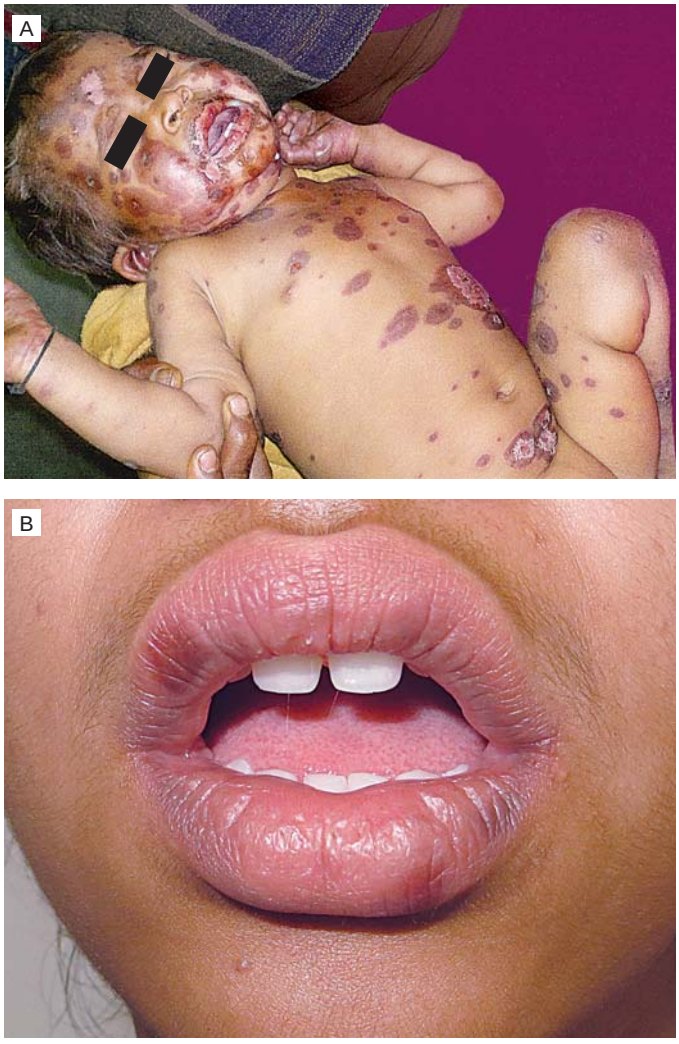

Fig. 44.8: (A) Multiple fixed drug eruption on lips in a HIV infected child; (B) Subtle mucosal lesions of FDE on lips in a child.

DIAGNOSIS OF DRUG REACTIONS

Diagnosis of drug reaction in children is based clinically on complete history and examination. Differentiating drug reactions from other exanthematous eruptions is challenging and of interest to pediatricians as they mimic viral exanthem. Few of the clinical features to differentiate drug reaction from viral exanthem are illustrated in Table 44.4. There are no specific investigations to diagnose drug reactions. Rechallenge can be done to eliminate the suspected drug.

MANAGEMENT OF DRUG REACTIONS

The mainstay of treatment in suspected drug reactions is removal of the offending drug. Majority of the drug reactions are not serious and resolve within few weeks of stopping the medications. It is important to weigh the risk–benefit ratio if the drug is necessary. Nonsevere-type drug reactions require only symptomatic treatment. Bland emollients, topical steroids and oral antihistamines relieve the pruritus associated with drug reactions. Management of SCARs in children is outlined in Table 44.5.[33–36] Counselling parents about the potential risk of drug reactions, avoidance of offending drug and other cross-reactive drugs is important. Parents should be advised to carry small diary regarding drug allergies and inform their pediatricians at every visit.

Table 44.4: Differentiating features between drug reactions and viral exanthem

Viral exanthem	Drug reaction
Constitutional symptoms are present	Constitutional symptoms are less
Onset of lesions starts from face, progresses to trunk and extremities, and resolves in same pattern	Abrupt onset of skin lesions
Pruritus absent	Pruritus present
Maculopapular rash	Dusky erythema
Palms and soles may/may not involved	Palms and soles involved
Systemic involvement is less	Systemic involvement is more common

Table 44.5 Management of SCARs in children

- Withdrawal of offending drug
- Supportive therapy
  - Bland emollients and dressings
  - Correction of fluid and electrolyte imbalance
  - Protein-rich diet
  - Maintenance of temperature
  - Prevention of skin trauma and infection
- Lubricants for eye care in TEN
- Topical and oral antibiotics to treat secondary infection
- Systemic corticosteroids: SJS, DHS, severe AGEP, SSLR, angioedema; dose: 1–2 mg/kg body weight for 2–3 weeks to 2 months in tapering doses
- Systemic corticosteroid in TEN is controversial
- IV immunoglobulin is the treatment of choice in TEN; it is given at the dosage of 0.1–0.5 g/kg daily for 4 days
- Cyclosporine: Treatment for TEN; dose: 3–6 mg/kg/day for 2–3 weeks
- Other immunosuppressants (second line of therapy): Cyclophosphamide, plasmapheresis, pentoxifylline, infliximab

TEN - toxic epidermal necrolysis; SJS - Stevens–Johnson syndrome; DHS - drug hypersensitivity syndrome; AGEP - acute generalized exanthematous pustulosis; SSLR - serum sickness–like reaction; IV - intravenous.

LEARNING ESSENTIALS

- CADRs are not uncommon in children, and one should have a good clinical knowledge about the clinical features and different reactions associated with drugs.
- Though maculopapular and urticarial eruptions are the most common clinical patterns of cutaneous reactions seen in children, other rare reactions should be kept in mind.
- SCARs should be monitored regularly to prevent complications.
- Counselling caregivers about the importance of notifying their child's drug allergy to pediatrician at every visit to prevent further exposures.

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Chapter

45

Cutaneous Adverse Drug Reactions in Pregnancy and Lactation

Iffat Hassan • Atiya Yaseen

SUMMARY

Drug prescribing and ensuring drug safety in pregnancy and lactation is of paramount importance as it can have effect on two lives, mother and newborn. Although the rate of adverse cutaneous drug reactions is low in pregnant and lactating females, these reactions can however be a cause of significant morbidity and mortality. Prompt differentiation of severe adverse cutaneous reactions from less serious ones is essential for a successful pregnancy outcome as well as for maternal and fetal well-being. A well directed patient-centric approach including a comprehensive history, detailed examination and a structured treatment plan is mandatory in the management of adverse drug reactions in pregnancy and lactation.

INTRODUCTION

"*Primum non nocere*" (Hippocrates) meaning "*First of all be sure you do no harm*" is so true and important when it comes to prescribing drugs. This is perhaps more important in the context of pregnancy and lactation.

Although adverse drug reactions have been reported in pregnancy (congenital anomalies) and lactation, there is paucity of literature on the occurrence of adverse cutaneous drug reactions during these periods. Table 45.1 provides a list of commonly used drugs in dermatology and their effects on the fetus and breast fed baby.[1-5] Despite significant safety concerns, pregnant and lactating women may be exposed intentionally or inadvertently to various prescription drugs for pregnancy-specific or non-specific indications. Of significance is the unforgettable thalidomide tragedy of the year 1961 when an unanticipated and serious drug reaction was observed in the babies delivered to mothers who had consumed thalidomide during their gestation. The drug interfered with babies` normal development, causing many of them to be born with phocomelia, resulting in shortened or absent limbs. One hundred sixty-one such babies were reported to be affected by the drug and by March 1962 the drug was completely banned in the countries where it was previously sold. Because of its adverse effects on the developing fetus, the dispensing of thalidomide is now regulated by the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S) program, which mandates the filing and education of all patients receiving the drug about its potential side effects.[6]

The paucity of data on CADRs during pregnancy and lactation could possibly be accounted by the restricted use of drugs during these periods and hence lesser occurrence of such reactions or due to under reporting. Nevertheless when drug reactions occur, the early identification of the condition, identifying the culprit drug and discontinuing it at the earliest remains an invaluable and corner stone approach in the prevention and management of CADR.[7,8]

MAGNITUDE OF THE PROBLEM

The incidence of ADRs in pregnant women has been reported to be 0.3%.[9] However, most estimates of the incidence of drug eruptions may be inaccurate, as many mild and transient eruptions are missed, and at the same time many skin disorders are falsely attributed to drug intake. In a review by Bonati et al.[10], USA and Europe reported an average of 4.7 drugs being used by pregnant women. Similarly, a 1996 survey of records of the French Health Insurance Service in a sample of 1000 women from southwest France reported that 99% received a prescription of at least one drug during pregnancy with a mean of 13.6 medications per woman.[11] A 2004 study

conducted across eight health organizations in USA analyzed 152531 pregnant women, of whom 64% were prescribed one drug other than a vitamin or mineral, with 39% receiving at least one drug during the first trimester.[12] Wettach et al.[13] in their study on pharmacovigilance in pregnant women have shown that most drugs are consumed during the 1st trimester (85.4%) followed by 2nd trimester (44.1%) and least in the third trimester (36.5%). Also, inadvertent exposure to drugs during pregnancy is a recognized factor in the causation of adverse drug reactions as 56% of pregnancies in the USA being unplanned, the first 4-6 weeks may be the vulnerable period for inadvertent drug intake.[14] Another contributing factor may be the drug exposure occurring before pregnancy, and may necessitate treatment to be instituted for necessary indications even after pregnancy is confirmed, thereby resulting in unwanted yet indispensable drug use during pregnancy.[15] In such cases, drugs which are well tolerated during non-pregnant state may be associated with the risk of CADRs as pregnancy is an independent risk factor for CADRs. Thus, the adequate information on drug safety in pregnancy is important to achieve two essential objectives i.e. the identification of potentially harmful exposures that might be avoided or managed, and the establishment of acceptable margins of safety for drugs whose benefits should overweigh the risks in the pregnant or lactating female.

WHY IS PREGNANCY AND LACTATION A RISK FACTOR FOR CADRs?

The drug pharmacokinetics and pharmacodynamics during pregnancy are altered by certain physiological changes. Figure 45.1 provides an overview of these factors.[16] Moreover, most drugs are of low molecular weight and if adequately absorbed through the maternal gastrointestinal tract can pass easily from the placenta to the fetus. Exchange occurs at capillaries of placental villi. Transplacental transport of drugs occurs by three mechanisms: (1) energy dependent active transport by specific carriers, (2) pinocytosis of low molecular weight drugs, and (3) simple diffusion. The mechanism of passage into breast milk is similar to those of transplacental transport of drugs, but agents must travel from perialveolar capillaries to the perialveolar interstitium. Subsequent transfer to milk occurs by the simple diffusion of drugs through the lipid barrier of mammary alveolar cells by passage of small molecules through membrane pores or by apocrine secretion.[17]

The fetus and the child are at the risk to the maternally consumed drugs during pregnancy or lactation. First trimester intake of drugs most commonly results in fetal teratogenicity, whereas ADRs in the neonatal and infantile period are more commonly encountered when the drugs are taken in the second or third trimesters.[18] Similarly, most drugs are excreted in the breast milk increasing the chances of developing adverse drug reaction in the breastfed child.[19] Table 45.1 provides information on some of the drugs commonly used during pregnancy and lactation and their effects on the fetus and breast fed infants. The factors determining the safety of drugs during breast feeding are enumerated in Table 45.2.[20] Also women are more susceptible to develop drug reactions than men. Hepatic enzyme CYP3A4 is more active in females. The pharmacodynamic gender differences are more common with cardiac and psychotropic drugs like chlorpromazine and fluspirilene, which are more effective in females.[21]

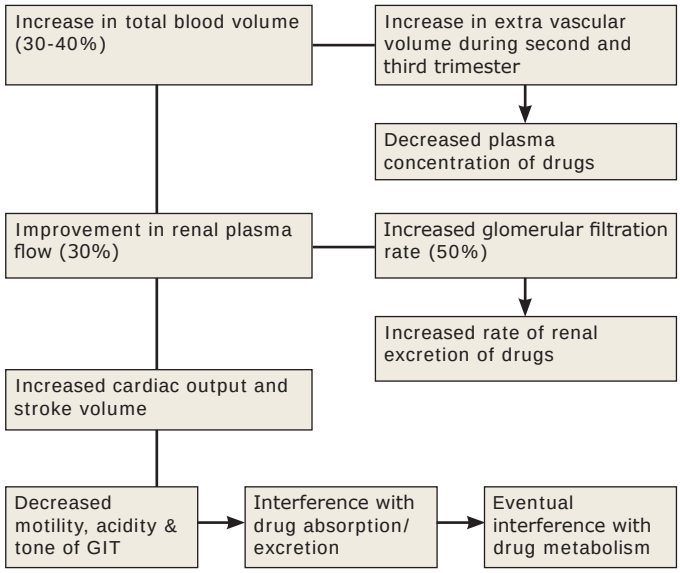

Fig. 45.1: Flow chart depicting factors affecting drug pharmacokinetics & pharmacodynamics during pregnancy.

Table 45.1: Effects of commonly used dermatological drugs on the fetus and breast fed baby[1-5]

Drug	FDA category	Potential adverse effect on fetus	Side effects on breast fed infant
Adrenocorticosteroids	C	Cleft palate and adrenal suppression in humans although no teratogenic effect has been reported.	Unlikely to cause any adverse effects on the breast fed infant.
Ampicillin	B	None known.	May lead to sensitization, diarrhoea, candidiasis, skin rash in infant.
Antihistamines			Small risk of unusual excitement or irritability in infants.
Aspirin	C	Increased risk of post maturity and premature closure of fetal ductus arteriosus when used in late pregnancy.	Risk on infant platelet function.
Azathioprine	D	No known teratogenicity but fetal immune system could be affected.	No problems documented, but breast feeding not recommended.
Chloroquine	C	Congenital deafness, fetal CNS damage, abnormal retinal pigmentation and hemorrhage.	No documented problems, but breast feeding not recommended.
Cephalosporin	B	None documented.	May change bowel flora in breast fed infant.
Cimetidine	C		Can suppress gastric acidity, inhibit drug metabolism, and can cause CNS stimulation.
Clofazimine	C	Crosses placenta, causing deep pigmentation of skin at birth.	Skin and fatty tissues of animal off springs become discolored 3 days after birth.
Cyclophosphamide	D	Fetal malformations like skeletal defects and dysmorphic features have been reported.	May lead to transient neutropenia.
Cyclosporine	C	No teratogenic effects reported at therapeutic doses.	Potential for hypertension, nephrotoxicity and malignancy in the infant.
Danazol	D	Clitoral hypertrophy, labial fusion, urogenital sinus defect, vaginal atresia and ambiguous female genitalia have been reported with long term therapy.	May cause virilization.
Dapsone	C	No known adverse fetal effects.	May cause hemolytic anemia in G6PD deficient infants.
Erythromycin	B	None known.	May cause diarrhoea in infant.
Estrogens	X	No increased risk of anomalies.	Gynecomastia reported in male infant.
Fluorouracil	D	First trimester use has resulted in skeletal abnormalities, hypoplasia of aorta, lungs, thymus and gastrointestinal and urinary tract. Cyanosis and clonus have been associated with third trimester use.	Breast feeding not recommended although no documented adverse effects.
Griseofulvin	C	Placental transfer at term, use not recommended in pregnancy.	None known.
Ibuprofen; Naproxen	B	May cause closure of ductus arteriosus or prolong labour when used in late pregnancy.	None known.

(Continued)

Table 45.1: Effects of commonly used dermatological drugs on the fetus and breast fed baby[1-5] (Continued)

Drug	FDA category	Potential adverse effect on fetus	Side effects on breast fed infant
Iodides	D	Goitre, fetal encephalopathy	May cause skin rash and thyroid suppression in infants.
Isoniazid	C	Psychomotor retardation, convulsions, myoclonus reported when used in combination with other drugs but none reported when used alone.	No documented problems but hepatotoxic metabolite found in breast milk.
Ketoconazole	C	No side effect reported when used in pregnant females.	Kernicterus in nursing infant.
Methotrexate	D	Potent teratogen in first trimester with multiple skeletal and neurologic defects reported.	Breast feeding not recommended although secreted in low concentrations in breast milk.
Metronidazole	B	No known teratogenicity in humans.	Breast feeding may be resumed 48 hours after completion of treatment.
Penicillin	B	None known.	May lead to sensitization, diarrhoea, candidiasis, skin rash in infant.
Phenytoin	D	Depletion of Vitamin K dependant factors and hemorrhagic diseases of new born. Increased risk of neonatal extrarenal Wilms' tumor, ganglioneuroblastoma, mesenchymoma and neuroblastoma. Fetal hydantoin syndrome encompassing abnormalities of fingers, toes and craniofacial defects, increased risk of cleft lip and palate, cardiac anomalies.	No documented adverse effects but breast feeding not recommended.
Progesterone	D	Masculinization of female fetus if taken beyond 8 weeks of gestation.	Causes suppression of lactation.
Psoralen, PUVA	C	Unknown effect in humans. Should be used only when indicated.	Should be avoided by nursing mothers.
Sulfonamides	C	Jaundice and kernicterus in fetus	Risk of kernicterus in the first 2 months of life.
Tetracycline	D	Staining of deciduous teeth if administered beyond third month of gestation.	Tooth staining, possible decreased skeletal growth, photosensitivity reactions, vestibular disturbances.
Thalidomide	X	Known human teratogen, with phocomelia, Amelia, hypoplasticity and absence of bones, external ear and eye abnormalities, facial palsy, congenital heart defects, alimentary tract, urinary tract and genital malformations as the reported adverse effects.	Effect on breast fed unknown but is not recommended in nursing mothers.
Vitamin A derivatives		Teratogenic effects on CNS, eye, ear, palate, heart, bones.	No known adverse effects but use in lactation not recommended.

FDA drug risk categories include: B- Fetal safety established in animal studies but lack of adequate and well controlled studies in pregnant women; C- Adverse effects on foetus in animal studies, no well controlled and adequate studies in humans, but potential benefits may outweigh the risk; D- Risk shown in human studies, but potential benefit may warrant use despite potential risks; X- Contraindicated.

Table 45.2. Factors which determine the safety of drugs during breast feeding[20]

Breast milk composition	Protein and lipid concentration Colostrum vs post-colostrum
Maternal factors	Hepatic and renal function Dose and duration of treatment
Infantile factors	Age Volume of milk intake Hepatic and renal function
Drug-related factors	Molecular size pKa Half life Bioavailability Water and lipid solubility Safety profile Route of administration Effect on milk production

CLINICAL PRESENTATIONS

Although the CADRs seen in the general population can be encountered in pregnant and breast feeding females as well and there are no drug reactions specific to these groups, a few patterns have been reported in literature and are detailed below.

Fixed Drug Eruptions

A fixed drug eruption characteristically recurs in the same site or sites each time the drug is administered; however, the number of involved sites may increase. A neutrophilic FDE has been described in a 27 year old pregnant female.[22]

Urticaria, Angioedema and Anaphylaxis

Angioedema is rarer than urticaria, and is twice as common in females as in males. Although there is no published data regarding the incidence of urticaria and angioedema in pregnancy but since it occurs in young women its incidence is probably the same or even greater than in the general population. Estrogen and progesterone levels, which dramatically rise in pregnancy, probably play a role in causation of urticarial rashes and angioedema.[23] A breast fed infant developed acute urticaria and malaise due to mother's parental intake of meglumine antimoniate for cutaneous leishmaniasis. The symptoms resolved in 24 hours after discontinuing breast feeding and receiving a single dose of antihistamine.[24]

Vasculitis

It develops 7-21 days after a new drug is administered and is characterized clinically by palpable purpuras over the legs. Other clinical presentations include erythematous macules, hemorrhagic vesicles, papules, wheals, blisters, ecchymosis and large palpable nodules. Two cases of drug induced leukocytoclastic vasculitis (LCV) in pregnancy have been reported in literature. In one of the cases, at week 14 prophylactic administration of ritodrine for 10 days following genetic amniocentesis was followed by fever, epigastric abdominal pain, polyarthritis, microhematuria, and purpura at week 16 and revealed LCV in biopsy. The second case was that of a 34-year-old pregnant woman who had developed polyarthralgias and polyarthritis after receiving ritodrine following genetic amniocentesis in her second gestation. Five days later, she presented with fever, polyarthritis, and purpura. A skin biopsy demonstrated LCV.[25]

Serum Sickness

It is a type III immune complex-mediated reaction, and occurs between 5 days and 3 weeks after initial exposure. It is constituted by fever, urticaria, angioedema, joint pain and swelling, lymphadenopathy, and occasionally nephritis or endocarditis, with eosinophilia. Complement (C3 and C4) levels are markedly decreased.[26,27] A serum sickness like reaction has been described in a 26-year-old pregnant female due to reintroduction of a single dose of infliximab (5 mg/kg) for relapse of her ulcerative colitis in the 32nd gestational week.[28]

Acute Generalized Exanthematous Pustulosis (AGEP)

This clinical entity appears in the intertriginous areas or in the face as sudden onset of a diffuse scarlatiniform erythema. Fever with an acute pustular eruption which resolves in <15 days, with lamellar or punctiform desquamation is quite characteristic. Numerous cases of acute generalized and localized exanthematous pustulosis have been reported in pregnancy and have been attributed to drugs like amoxicillin clavulanate, paracetamol and clindamycin.[29-32]

Erythema Multiforme (EM) / Stevens Johnson Syndrome (SJS) / Toxic Epidermal Necrolysis (TEN)

Erythema multiforme is characterized by symmetrical and acrally distributed, typical or raised atypical target lesions, with either absence or limited mucosal involvement, and recurrent episodes lasting less than 4 weeks. On the other hand, SJS, TEN and overlap (SJS/TEN) are severe variants in spectrum of epidermal necrolysis.[33] A successful pregnancy outcome following penicillin induced SJS has been reported.[34] A large majority of patients who develop SJS/TEN in pregnancy are human immunodeficiency virus-positive and nevirapine is the most common

drug incriminated in such cases.[35] A high survival rate of both mother and fetus has been reported in TEN in pregnancy. Vaginal stenosis and adhesions, endometriosis and telangiectasia are among the long term complications.[36-38]

APPROACH TO CADRs IN PREGNANT AND LACTATING WOMEN

It is imperative to have a high index of suspicion about the possibility of a CADR in a pregnant or a lactating woman. The approach to a pregnant or lactating female with a cutaneous adverse drug reaction is essentially based on the same principles as that for the general population. Determining the safety of medications administered during pregnancy and breast feeding is an important factor as it puts two lives at risk. Apart from prescriptional medication, evidences show that use of over-the-counter medications is higher during pregnancy than in the pre conception period. A careful analysis of drug exposure must be undertaken, and medications of all types, whether allopathic, homeopathic, ayurvedic, natural or traditional etc., administered by any route, taken on a daily or intermittent basis must be considered especially those consumed in the preceding 8 weeks.

Ascertaining drug causality by various in- vivo and in- vitro methods should be avoided during pregnancy due to safety reasons. De-challenge should be the only means of identifying CADRs during pregnancy and lactation as the safety of other tests like re-challenge, patch, prick and in vitro testing has not adequately been documented.

MANAGEMENT

Management of CADRs in pregnancy and lactation usually follows the same protocol as in the general population. A thorough history taking, identifying the clinical pattern, ruling out other confounders, effect of dose reduction/stoppage (de-challenge) to identifying the culprit agent and stopping/ substituting it and prevention of reaction in future by patient counselling are the essentials of management during pregnancy like in other states. The specific management particularly in severe cutaneous adverse drug reaction (SCAR) may differ due to safety concerns of drugs during pregnancy.

Symptomatic treatment like antihistamines may be used safely for minor reactions. Table 45.3 gives an account of pregnancy and lactation category of various antihistamines. The American College of Obstetricians and Gynecologists (ACOG) and The American College of Allergy, Asthma and Immunology (ACAAI) have recommended chlorpheniramine and tripelennamine as the antihistamines of choice for pregnant women. They also recommend cetirizine and loratadine after the first trimester in patients who cannot tolerate or do not respond to maximal doses of chlorpheniramine or tripelennamine.[40,41] First generation antihistamines should be used with caution during lactation and children should be monitored for signs of irritability and drowsiness.[42] Non-sedating second generation drugs are preferred.

Table 45.3: Category of various antihistamines in pregnancy and lactation.

FIRST GENERATION ANTIHISTAMINES		
Drugs	**FDA category (Pregnancy)**	**Hale category (Lactation)[42]**
Chlorpheniramine	B	L3
Cyproheptadine	B	L3
Dexchlorpheniramine	B	L3
Hydroxyzine	C	L1
Promethazine	C	L2
Tripelennamine	B	L4
SECOND GENERATION ANTIHISTAMINES		
Drugs	**FDA category**	**Hale category (Lactation)**
Cetirizine	B	L2
Fexofenadine	C	L2
Loratadine	B	L1
Levocetirizine	B	L2
Desloratadine	C	L2

FDA risk category: B - Fetal safety established in animal studies but lack of adequate and well controlled studies in pregnant women; C - Adverse effects on foetus in animal studies, no well controlled and adequate studies in humans, but potential benefits may outweigh the risk Dr. Hale's lactation risk categories include: L1 Safest, L2 Safer, L3 Moderately safe, L4 Possibly hazardous, L5 Contraindicated.

Specific treatment

Steroids may have to be used for life threatening reactions like SJS/TEN. However, adrenal suppression and cleft palate are the major concerns with the use of systemic corticosteroids in pregnancy. In general, steroids should be avoided in the first trimester, but may be valuable in the third trimester, where they also serve to fasten lung maturity. However, Stevenson[43] reviewed 6 retrospective reports of corticosteroid administration to 444 pregnant females and found that only 5 neonates suffered from cleft palate. Another report has also not confirmed an increase of cleft palate or other teratogenic effects.[44] Moreover, maternal doses of prednisolone of up

to 20 mg/day have been shown to result in less than 0.1% of the ingested dose reaching the infant which is equivalent to less than 10% of the infant's endogenous cortisol production.[45]

Intravenous immunoglobulins and cyclosporine have been tried in individual cases.[46] While intravenous immunoglobulins have been tried safely in pregnant females with TEN, there is not much literature on the use of cyclosporine in the treatment of TEN in pregnancy. Neonatal side effects have been observed in pregnant renal transplant recipients, who require long term treatment. However, the drug can be safely used in TEN in pregnancy as TEN does not require prolonged treatment with cyclosporine.[47]

Vaginal moulds smeared with corticosteroids/lubricant gel can be used intravaginally to prevent adhesions/stenosis in cases of SJS/TEN.[47]

RECORDING CADRs IN PREGNANT AND LACTATING FEMALES: THE NEED FOR A BETTER PHARMACOVIGILANCE

This can be done using individual clinician's case reports, centralised adverse event reporting system or pregnancy drug exposure registries. However, the concern with these registries is that most of the transitory and less severe cases of CADR will be missed, thus providing false data. It is important to realize that no single study design or methodology is sufficient to assure that a particular medication can be used safely in pregnancy or lactation. Therefore, a coordinated and systemic approach to evaluate new medications, both at the national and an international level, could contribute to more effective pharmacovigilance for CADRs in pregnancy and lactation and may provide information regarding the frequency with which a specific morphologic pattern may be related to a particular drug.

The decision to withhold a drug in these high risk groups or to continue it must be based on the medical necessity of the drug, the possibility of alternative agents, and the severity of the cutaneous reaction. Interdisciplinary approach should be followed involving all stakeholders in the management of cutaneous or systemic ADR.

LEARNING ESSENTIALS

- Physicians must exercise extreme caution in prescribing drug(s) during pregnancy and lactation as it puts two lives under risk. Most of the drugs are of low molecular weight and if adequately absorbed through the maternal gastrointestinal tract can pass easily from the placenta to the fetus during pregnancy.
- The decision to withhold a drug in high risk groups or to continue it must be based on the medical necessity of the drug, the possibility of alternative agents and the severity of the cutaneous reaction. Interdisciplinary approach should be followed involving all stakeholders in the management of cutaneous or systemic ADR.
- In case of severe reactions, the offending drug must be unequivocally withheld from the pregnant or lactating female. Steroids, intravenous immunoglobulins and cyclosporine can be safely used in these patients.

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Chapter

46

Clinically Important Adverse Drug Interactions in Dermatology

Nidhi Shah • Neil H. Shear

SUMMARY

Drug interactions, though common, are not always associated with adverse outcomes. Widespread use of systemic drug therapy in dermatology combined with prevalence of polypharmacy necessitates vigilance on the clinician's part. Knowledge of the mechanisms of drug interactions helps the clinician to be aware of the possibility of such an event in a given situation. This chapter focuses on the general mechanisms of drug interactions, and interactions involving some common drugs, as knowing all the interactions can be a formidable task. There are some commonly used drugs that often cause drug interactions. As initial evidence for drug interactions usually comes from case reports, clinicians can have an important role in providing information.

Increasing use of systemic drugs in the dermatologic practice and prevalence of polypharmacy increase the potential for drug interactions. Drug interaction occurs whenever one drug affects the pharmacokinetics, pharmacodynamics, efficacy, or toxicity of another drug. Pharmacokinetic interactions involve the processes by which the drugs are absorbed, distributed, metabolized and excreted (ADME). Pharmacodynamic interactions occur when one drug affects the action of another drug, which may be synergistic or antagonistic or when they compete for the receptor directly related to the pharmacologic response. Majority of drug interactions in dermatology practice are pharmacokinetic in nature. Drug interactions when undesirable become adverse drug interactions.

Drug interactions are usually predictable and follow the 80:20 rule i.e. 20% of drugs cause 80% of interactions. Hence, the knowledge of the mechanism by which these drugs cause interactions is helpful in the clinical practice. Adverse drug interactions may lead to increased toxicity, decreased efficacy, or both. Knowledge of the interactive properties of drugs can help prevent serious adverse drug interactions. Nonprescription drugs, herbal or alternative medicines and foods (e.g. grapefruit juice) may also be implicated in drug interactions.

IMPORTANT LEARNING RESOURCES

It is important to be aware of those patients who are truly at risk (Table 43.1).[1] It is not possible for individual clinician to remember all drug interactions; however, it is prudent to understand how to use the drug interaction information provided by computers, books and other sources. One of the best sources is *The Top 100 Drug Interactions: A Guide to Patient Management*, 2017 edition.[2] This small pocketbook, which is revised every year, is a treasure to have in the clinic as it contains the most up-to-date adverse drug reactions and does not broadly apply an interaction to drugs as a class. Instead, this book teases out the subtle differences in drug interaction potential among drugs within a given class, for example macrolide antibiotics. This type of information is lacking in most textbooks and drug interaction software. Another source is *Litt's Drug Eruption and Reaction Manual*, 23rd edition.[3] This book lists important drug interactions along with the adverse reactions associated with each drug.

RISK ASSESSMENT IN THE CLINICAL OUTCOME OF DRUG INTERACTIONS

Predicting drug interactions is possible when those agents likely to produce alterations in drug metabolism via inhibition or induction of the cytochrome P450 (CYP) system are recognized. Many

of these drug combinations can be administered safely with appropriate dosage adjustments, or by substitution with another member of the drug class with less potential for drug interactions.[4] Drug interactions occur commonly; however, in many cases, their effects do not result in clinically significant outcomes. The clinical outcome of most drug interactions is highly situational. Emphasis should be placed on those factors that increase or reduce the risk for an adverse drug interaction for a given patient (Box 46.1).

Box 46.1: Patient risk factors for drug interactions

- Multiple medications
  - Polypharmacy
- Demographic risk factors
  - Female gender
  - Extremes of age (very young and elderly)
- Major organ dysfunction (especially when multiple medical problems)
  - Liver dysfunction
  - Renal insufficiency
  - Congestive heart failure
- Metabolic and endocrine risk factors
  - Obesity
  - Hypothyroidism
  - Hypoproteinemia
- Pharmacogenetic risk factors
  - Slow acetylator phenotype
  - Reduced TPMT activity
  - Other genetic polymorphisms
- Other medical issues
  - Hypothermia
  - Hypotension
  - Dehydration

TPMT - thiopurine methyltransferase.

POLYMORPHISMS

Major source of interindividual differences in drug metabolism are genetic polymorphisms, which are inherited significant variations in the activity of drug-metabolizing enzymes. These polymorphisms exist for various CYP isoforms and other enzymes involved in drug metabolism. There are also interethnic differences in drug metabolism, differences in the expression of CYP isoforms and glucuronyltransferases and different frequencies of genetic polymorphisms.[5] In many cases, it is possible to determine an individual's genotype.[6]

THERAPEUTIC INDEX

The medications most likely to be involved in drug interactions must be evaluated. Interactions occur with drugs that have a narrow margin of safety, hence a narrow therapeutic index. Some examples of drugs with the potential for such serious interactions due to a narrow therapeutic index include warfarin, digoxin, monoamine oxidase inhibitors, methotrexate and cyclosporine A (CsA).

MECHANISM OF DRUG INTERACTIONS

ABSORPTION

Drug interactions in the gastrointestinal (GI) tract can result in decreased absorption. This reduces the bioavailability or the amount of drug available to the systemic circulation and results in subtherapeutic serum concentrations. The mechanisms of most drug interactions that alter absorption involve (1) the formation of drug complexes that reduce absorption, (2) alterations in gastric pH, or (3) changes in GI motility that alter transit time.[7]

Drug Complexes

Common drugs that form complexes with other drugs include antacids, sucralfate and cholesterol-binding resins. A significant interaction occurs between multivalent cations, such as calcium, aluminum, iron and magnesium; tetracyclines and fluoroquinolones. These metal ions chelate these antibiotics in the GI tract, thus impairing absorption.[8] There is an 85% reduction in the absorption of ciprofloxacin when ingested 5–10 minutes after a dose of an aluminum hydroxide/magnesium hydroxide antacid.[9] Alendronate, a bisphosphonate for the prevention and treatment of osteoporosis, forms complexes with many drugs, thereby further reducing its already low oral absorption.[10] Mycophenolate mofetil can form complexes with antacids, cholestyramine, colestipol and iron.[11,12]

Alterations in Gastric pH

Drugs that increase gastric pH, such as proton pump inhibitors, antacids, and H_2 antihistamines, may reduce the absorption of drugs such as ketoconazole and itraconazole, which are absorbed best in an acidic environment.[13] However, variations in gastric pH do not seem to affect absorption of fluconazole or voriconazole.[14]

Gastrointestinal Motility

Drugs that affect GI motility, such as anticholinergic agents, may reduce the rate, but not the extent, of absorption. An overall reduction in the extent of drug absorption has more clinical significance.[15]

Enterohepatic Recirculation

Some drugs may interfere with the enterohepatic recirculation of a substrate drug. When the substrate drug is excreted into the GI tract, the drug inhibitor can bind to it and prevent its reabsorption back into the systemic circulation. The bound substrate drug is excreted in the feces, shortening its half-life and reducing the total absorption. An example of this is the concurrent administration of warfarin and cholestyramine. The half-life of warfarin is shortened by oral cholestyramine.

P-GLYCOPROTEIN

P-glycoprotein (PGP) is an ATP-dependent plasma membrane glycoprotein belonging to the superfamily of ATP-binding cassette transporters that function as drug transporters and hence affect both drug absorption and elimination.[16] High levels of PGP are found in superficial columnar epithelial cells of the small intestine, apical surface epithelial cells of the proximal tubules of the kidney and the biliary canalicular membrane of hepatocytes. PGP is also detected in high concentrations in the epithelial cells of capillaries of the blood–brain barrier, testes, uterus and placenta.

These membrane-bound transport systems appear to have developed as a mechanism to protect the body from harmful substances. It appears that PGP acts as a pump whereby efflux of drugs from the cell membrane or cytoplasm is powered by the energy from ATP hydrolysis. The range of substrates, inhibitors and inducers for PGP is vast and expanding (Box 46.2 and 46.3).

Box 46.2: P-glycoprotein substrates[19,20]

- Antihistamines: Fexofenadine
- Antiemetics: Domperidone, ondansetron
- Antimicrobials: Ciprofloxacin, erythromycin, ivermectin, quinolones, rifampin, posaconazole
- β-Blockers: Bisoprolol, nadolol, propranolol, timolol
- Calcium channel blockers: Diltiazem, verapamil
- Cardiac agents: Amiodarone, digoxin, quinidine
- Chemotherapeutic agents: Actinomycin D, daunorubicin, doxorubicin, etoposide, mitomycin C, paclitaxel, taxol, vinblastine, vincristine
- HIV protease inhibitors: Indinavir, nelfinavir, ritonavir, saquinavir
- Immunosuppressive agents: Cyclosporine, tacrolimus
- Rheumatologic agents: Colchicine, methotrexate, quinine
- Statins: Atorvastatin, lovastatin, pravastatin
- Miscellaneous: Cimetidine, lidocaine, loperamide

Box 46.3: P-glycoprotein inhibitors[19,20]

- Antimicrobials: Clarithromycin, erythromycin, itraconazole, ivermectin, ketoconazole, mefloquine, ofloxacin, rifampin
- Psychotropic drugs: Amitriptyline, chlorpromazine, desipramine, doxepin, fluphenazine, haloperidol, imipramine
- β-Blockers: Carvedilol, propranolol
- Calcium channel blockers: Diltiazem, felodipine, nicardipine, verapamil
- Cardiac medication: Amiodarone, dronedarone, dipyridamole, propafenone
- Immunosuppressive agents: Cyclosporine A, tacrolimus
- Protease inhibitors: Ritonavir
- Steroid hormones: Progesterone, testosterone
- Miscellaneous: Disulfiram, grapefruit juice, tamoxifen

Although the inhibition and induction of intestinal CYP3A enzymes from metabolic processes result in direct changes in drug absorption, the inhibition and induction of PGP primarily affects the rate of drug absorption.[17] If one drug is a substrate of both PGP and CYP3A4 (both found in proximity to the intestinal wall), and a second drug that is an inhibitor of both PGP and CYP3A4 (e.g. ketoconazole, erythromycin) is added, then the first drug will be allowed in increased amounts. Since CYP3A4 is inhibited, levels of unmetabolized drug will enter the blood. The effect of PGP blockade is to "open the gates" so that the later actions of CYP3A4 inhibition will be increased. However, the involvement of CYP3A4 and a PGP in drug interactions is not always complementary.

Inhibitors of PGP reduce the renal and nonrenal elimination of digoxin. Digoxin plasma concentrations may increase two- to four fold, but larger increases may occur, especially with potent PGP inhibitors such as itraconazole or ketoconazole. Alterations in digoxin levels should be monitored, if one of these antifungals is initiated, discontinued, or changed in dosage. Adjustments in digoxin dose may be needed, and a digoxin level should be obtained within 10 days, which is the time for digoxin to achieve a new steady state.

PGP inhibitors are also developed to exploit the increased absorption of some chemotherapeutic drugs.[18]

DISTRIBUTION

Highly Protein-Bound Drugs

Drugs that are highly protein bound (>90%) may cause drug interactions based on alterations

in drug distribution. When one drug displaces another from plasma protein–binding sites, the free serum concentration of the displaced drug is increased and its pharmacologic effect increases. However, the unbound fraction of the drug (free drug) is not only more available to sites of action but is also more readily eliminated. Any enhanced pharmacologic effect occurs only transiently because of a compensatory increase in elimination, and the clinical effect of displacement interactions is usually negligible. Therefore, these interactions involving drug displacement from binding proteins tend to be self-limiting.[21]

Therefore, it is safe to say that if a patient does not manifest an adverse event from the combination therapy in the first week or so of administration, an adverse event probably will not occur. In practice, protein-binding displacement interactions do not produce clinically important changes in drug response unless the drug also has a limited distribution in the body, is slowly eliminated, or has a narrow therapeutic index. For this reason, protein-binding displacement interactions may assume greater importance when the displacing inhibitor also reduces the elimination of the substrate drug. A good example of this principle involves interactions with nonsteroidal anti-inflammatory drug (NSAID) and methotrexate.[21]

Medications most susceptible to interactions based on changes in drug distribution involving displacement from binding proteins include warfarin, sulfonamides and phenytoin.[21]

METABOLISM

The most clinically relevant drug interactions are caused by alterations in drug metabolism. When drugs are administered, they are metabolized through a series of reactions to enhance drug hydrophilicity (water solubility) and facilitate drug excretion. These drug biotransformation reactions are grouped into two categories: Phase I and phase II. Phase I reactions involve intramolecular changes, such as oxidation, reduction, and hydrolysis, which make the drug somewhat more polar. Phase II reactions are conjugation reactions in which an endogenous substance combines the functional group derived from phase I reactions to produce a highly polar drug conjugate (which is much more water soluble) that can be readily eliminated from the body. Examples of these phase II reactions include glucuronidation and sulfonation.

The metabolic products are often less active than the parent drugs, or more commonly are inactive. However, some metabolites may have enhanced activity or toxic effects, including roles in carcinogenesis, mutagenesis, or teratogenesis.[22] Therefore, biotransformation may include both detoxification and toxification processes. An example of this principle would be cyclophosphamide. This drug is actually a prodrug metabolized to phosphoramide mustard (the active form of the drug) and to a second metabolite acrolein, which induces bladder toxicity.

The most important organ of biotransformation is the liver, although other organs (e.g. the small intestine and lung) can contribute to overall drug metabolism, depending on the route of administration. Drug-metabolizing enzymes include the CYP mixed-function oxidases, thiopurine methyltransferase (TPMT), *N*-acetyltransferase, epoxide hydrolases and glutathione synthetase.[23]

EXCRETION

Another mechanism for drug interactions involves a change in drug disposition due to altered renal clearance. An example is that of an NSAID that inhibits the renal elimination of methotrexate. Probenecid inhibits the active renal tubular excretion of methotrexate.

CYTOCHROME P450–BASED DRUG INTERACTIONS

CYP enzymes are the most important drug-metabolizing enzymes. They are present in the endoplasmic reticulum of many types of cell but are at highest concentration in hepatocytes.[24] These heme-containing proteins exist as gene superfamilies, with the encoded isoforms exhibiting distinct, but overlapping, substrate specificities and isoform-specific regulatory and pharmacogenetic properties. The nomenclature uses a three-tier classification consisting of the family (40% homology in amino acid sequence), the subfamily (55% homology) and the individual protein (e.g. CYP2D6).[25]

The metabolism of a drug by a specific isoenzyme indicates that it is a substrate for that enzyme. Many drugs serve only as substrates and produce no significant enzyme inhibition or induction. It is entirely possible for a drug to be a substrate for one enzyme and inhibit or induce another enzyme that is not involved with its own metabolism. The interactions that may result are affected by genetics (polymorphic genes cause particular enzymes to be less effective, 2D6 being an example), drugs (a drug may inhibit or induce a cytochrome, or interfere in the chemical pathway of another drug, e.g. ketoconazole reduces cyclosporine metabolism by inhibiting CYP3A4), chemicals (dioxin is an inducer of CYP3A4 while a food such as grapefruit juice is an inhibitor

of CYP3A4) and the environment (cigarette smoke is an inducer of CYP1A2).[25]

An increased understanding of CYP drug metabolism has solved much of the mystery behind drug interactions. While there are approximately 60 genes that encode CYP isoforms, over 90% of drug oxidation can be attributed to 6 main cytochromes: CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4.[26] One-third to one-half of drug metabolism can be attributed to CYP3A4. This statistic indicates the greater likelihood of drug–drug interactions involving CYP3A4. The isoform CYP2D6 is involved in about one-fourth of all drug metabolism. The concept that most drug oxidation reactions are catalyzed primarily by a small number of CYP enzymes is important in that approaches to identifying drug–drug interactions become more feasible, both in vitro and in vivo. Each CYP isoform can oxidize several drugs and has wide substrate specificity. A drug may have a very high affinity for one particular CYP isoform. Under physiologic conditions, this CYP isoform almost exclusively catalyzes the drug's oxidation. Many commonly used drugs have been identified as substrates for specific CYP isoforms.[27] Examples include CsA and finasteride, which are substrates of CYP3A4.

The successful application of information regarding CYP to prevent drug interactions and improve the therapeutic risk–benefit ratio can occur only if we know which enzyme is responsible for the metabolism of a particular drug. Drug interactions are also made more predictable by determining which compounds induce and inhibit which specific P450 enzymes. Although knowing all of the major enzyme substrates, inhibitors, and inducers is a formidable task, Tables 46.1–46.5 are intended to summarize large amounts of this information.

Table 46.1: CYP1A2 selected substrates, inhibitors and inducers[25,30]

Substrates	Inhibitors	Inducers
Amitriptyline	Cimetidine	Barbiturates
Clomipramine	Ciprofloxacin	Carbamazepine
Caffeine	Clarithromycin	Omeprazole
Clozapine	Erythromycin	Phenobarbital
Desipramine	Fluvoxamine	Phenytoin
Fluvoxamine	Ketoconazole	Rifampin
Haloperidol	Norfloxacin	Ritonavir
Imipramine	Terbinafine	**Food and substances**
Propranolol	Ticlopidine	Brussels sprouts
Tacrine		Cabbage
Theophylline		Charbroiled foods
Warfarin		Cigarette smoking
Zileuton		
Zolmitriptan		

Table 46.2: CYP2C9 selected substrates, inhibitors and inducers[25,30]

Substrates	Inhibitors	Inducers
Diclofenac	Amiodarone	Barbiturates
Fluoxetine	Cimetidine	Carbamazepine
Fluvastatin	Clopidogrel	Ethanol
Ibuprofen	Fluconazole	Griseofulvin
Losartan	Fluvoxamine	Rifampin
Montelukast	Ketoconazole	
Phenytoin	Leflunomide	
Piroxicam	Omeprazole	
Sulfonamides	Ritonavir	
Tricyclic antidepressants	Sulfonamides	
Valproic acid	Trimethoprim	
Warfarin	Voriconazole	
Zafirlukast	Zafirlukast	

Table 46.3: CYP2C19 selected substrates, inhibitors and inducers[25,30]

Substrates	Inhibitors	Inducers
Citalopram	Cimetidine	Norethindrone
Cyclophosphamide	Felbamate	Prednisone
Diazepam	Fluconazole	Rifampin
Imipramine	Fluoxetine	
Indomethacin	Fluvoxamine	
Lansoprazole	Indomethacin	
Nelfinavir	Ketoconazole	
Nilutamide	Lansoprazole	
Omeprazole	Modafinil	
Pantoprazole	Omeprazole	
Progesterone	Paroxetine	
Proguanil	Ticlopidine	
Teniposide	Topiramate	
Warfarin	Voriconazole	

Cytochrome Induction

Many enzymes involved in drug biotransformation, including CYPs, are able to increase in amount and activity in response to substances known as inducers. The onset and offset of enzyme induction is *gradual* because the induction phase depends on the accumulation of the particular inducing agent and the subsequent synthesis of new enzyme. The offset depends on elimination of the inducer and decay of the increased enzyme levels.

Inducers may enhance parent drug metabolism, so that therapeutic efficacy is actually reduced if the parent drug is the active moiety. Alternatively, inducers may enhance the metabolism of a substrate to

Table 46.4: CYP2D6 selected substrates, inhibitors and inducers[25,30,31]

Substrates	Inhibitors	Inducers
Antidepressants: Amitriptyline, clomipramine, desipramine, imipramine, nortriptyline, trazodone, fluoxetine, paroxetine, fluvoxamine, citalopram, venlafaxine, mianserin, mirtazapine **Antipsychotics**: Thioridazine, perphenazine, zuclopenthixol, haloperidol, risperidone, clozapine, olanzapine, sertindole **Opiates**: Codeine, dextromethorphan, tramadol β-**blockers**: Alprenolol, bufuralol, metoprolol, timolol, pindolol **Antiarrhythmics**: Encainide, flecainide, propafenone **Miscellaneous:** Diphenhydramine, domperidone, donepezil, phenformin, debrisoquine	**Antidepressants:** Fluoxetine, paroxetine, sertraline, clomipramine, desipramine **Antipsychotic agents:** Haloperidol, thioridazine **Antidysrhythmics:** Amiodarone, dronedarone, propafenone, quinidine **Miscellaneous:** Terbinafine, cimetidine, ritonavir, bupropion, celecoxib, thioridazine, perphenazine, chloroquine, hydroxychloroquine	Carbamazepine, phenobarbital, phenytoin, isoniazid, rifampin

Table 46.5: CYP3A4 selected substrates, inhibitors and inducers[30]

Substrates	Inhibitors	Inducers
Antiarrhythmics: Amiodarone‡, digoxin‡ propafenone‡, quinidine‡ **Antimicrobial agents:** Erythromycin, rifampin **HIV-1 protease inhibitors:** Indinavir, nelfinavir, ritonavir, saquinavir **Anticonvulsants:** Carbamazepine‡, ethosuximide **Antidepressants:** Amitriptyline, doxepin, imipramine, sertraline **Benzodiazepines:** Alprazolam diazepam midazolam, triazolam **Calcium channel blockers:** Amlodipine, diltiazem, felodipine, isradipine, nifedipine, verapamil **Cancer chemotherapy:** Busulfan, cyclophosphamide, docetaxel, doxorubicin‡, etoposide, ifosfamide, paclitaxel, tamoxifen, vinblastine‡, vincristine‡ **H_1 antihistamines:** Astemizole*, fexofenadine†, loratadine†, terfenadine* **HMG-CoA reductase inhibitors:** Atorvastatin‡, cerivastatin*, lovastatin‡, simvastatin‡ **Hormonal agents:** Estrogens, oral contraceptives **Immunosuppressive drugs:** Corticosteroids, cyclophosphamide, cyclosporine, tacrolimus‡ **Proton pump inhibitors:** Omeprazole **Miscellaneous drugs:** Acetaminophen, codeine, cisapride*, dapsone†, enalapril, flutamide, losartan, pimozide‡, retinoic acid†, sildenafil, theophylline‡, voriconazole‡, zileuton‡, lidocaine, warfarin*‡	**Antibiotics:** Clarithromycin, erythromycin, metronidazole, norfloxacin, quinupristin, dalfopristin, troleandomycin **Azole antifungals:** Fluconazole (if >200 mg/day), itraconazole, ketoconazole‡, voriconazole **Calcium channel blockers:** Diltiazem, verapamil **HIV-1 protease inhibitors:** Indinavir, nelfinavir, ritonavir, saquinavir **SSRI antidepressants:** Fluoxetine fluvoxamine paroxetine sertraline **Other inhibitors:** Amiodarone‡, antiprogestins, cannabinoids, cimetidine, dronedarone, grapefruit juice, imatinib, interferon-γ‡, quinine, tacrolimus, tamoxifen	**Anticonvulsants:** Carbamazepine‡, ethosuximide, phenobarbital, phenytoin‡, primidone **Antituberculous agents:** Isoniazid, rifabutin, rifampin† **Other inducers:** Bexarotene, dexamethasone, griseofulvin, nefazodone, St. John's wort, ticlopidine, troglitazone

* Off market.
‡ Narrow therapeutic index.
† Used by dermatologists

active metabolites, with the potential for exaggerated toxicity. For example, the alkylating agent cyclophosphamide is a prodrug that requires metabolic activation to phosphoramide mustards for its therapeutic effect. Unfortunately, metabolic activation also leads to the formation of acrolein, which causes the bladder toxicity seen with this medication.[28]

Cytochrome Inhibition

Inhibition of drug metabolism is the most important mechanism for drug interactions because it can lead to an increase in plasma drug concentration, enhanced drug response and toxicity. In contrast to the time course seen with enzyme induction, inhibition of drug metabolism begins within the first one or two doses of the inhibitor and is maximal when a steady-state concentration of the inhibitor is achieved. Therefore, the time course for inhibitory actions is usually in terms of *days* not weeks.

Inhibitory interactions can be either competitive or noncompetitive. An example of *competitive* inhibition involves the tight binding of inhibitors such as ketoconazole, cimetidine, and macrolides to the heme moiety of the CYP isozyme. As long as the inhibitor occupies this specific site of the CYP, the substrate cannot be biotransformed.[29] As the concentration of the inhibiting drug increases, the degree of saturation of the isoenzyme increases. When the enzyme system is saturated, further metabolic activity by that enzyme system is limited. At that point, a patient becomes the equivalent of a poor metabolizer and concentrations of coprescribed medications begin to rise. The extent of inhibition of one drug by another depends on the affinity each compound has for the CYP isoform. In addition to the concentration of substrate required to saturate the system and the half-life of the inhibitor drug, competitive inhibition clearly depends on the affinity of the substrate for the enzyme being inhibited. The onset and offset of enzyme inhibition are dependent on the half-life and time to steady state of the inhibitor.

The significance of an elevated plasma level of a particular drug is determined largely by the therapeutic margin of the drug. Therefore, when considering the potential clinical relevance of an interaction, one must exercise more caution with drugs that have a narrow therapeutic range. Noncompetitive inhibition is less common and occurs when the enzyme is destroyed, inactivated, or changed by the inhibitor such that it can no longer metabolize the original substrate.

DRUG INTERACTION RISKS BY CATEGORY

Table 46.6 lists drug categories in which there are variable risks for drug interactions involving metabolism.

Table 46.6: Drug categories with variable risks for drug interactions

Drug class	Drugs with greater potential for interactions	Drugs with less potential for interactions
Antifungals	Azoles and triazoles (CYP3A4 inhibition)	Terbinafine
Macrolides	Clarithromycin Erythromycin	Azithromycin
Calcium channel blockers	Diltiazem Verapamil	Amlodipine Nifedipine
Fluoroquinolones	Ciprofloxacin Enoxacin	Levofloxacin Lomefloxacin Ofloxacin
H_2 antihistamines	Cimetidine	Famotidine Nizatidine Ranitidine
HIV-1 protease inhibitors	Ritonavir Indinavir	Saquinavir Nelfinavir
HMG-CoA reductase inhibitors	Simvastatin Lovastatin Atorvastatin Cerivastatin*	Pravastatin Fluvastatin
Foods	Grapefruit juice	Orange juice

* Off market.

Azole Antifungals

The azole antifungal agents include the original imidazoles, such as ketoconazole, in addition to the triazoles itraconazole, fluconazole and voriconazole. Ketoconazole and itraconazole require an acid milieu for absorption, as concomitant antacids, H_2 antihistamines, proton pump inhibitors (such as omeprazole) and didanosine significantly reduce absorption.

Azole antifungals are inhibitors of several CYP isoforms, particularly CYP3A4 (Tables 46.1–46.3). Ketoconazole is the strongest in vitro inhibitor of CYP3A4. Itraconazole is an inhibitor of CYP3A4, whereas fluconazole inhibits CYP2C9 significantly more than its minimal inhibitory role of CYP3A4, however, at doses more than 200 mg/day can cause inhibition of CYP3A4.

The substrates metabolized via these enzymes that can lead to moderate-to-severe drug interactions when coprescribed with azole antifungals are phenytoin, warfarin and CsA. Phenytoin concentrations were significantly increased 48 hours after fluconazole

administration, resulting from a 33% decrease in the clearance of phenytoin.[32] When the azole antifungals (especially ketoconazole and itraconazole) are administered with CsA, the concentrations of CsA are increased, requiring careful monitoring of CsA levels. Similarly, frequent monitoring of the international normalized ratio (INR) is required for patients on warfarin who require therapy with an azole antifungal. The azole antifungals (most importantly fluconazole) reportedly increase the anticoagulant effects of warfarin two- to three fold.

Azole antifungals interfere with the metabolism of benzodiazepines, such as triazolam and midazolam, leading to increased levels and excessive sedation. There is also decreased metabolism of HMG-CoA reductase inhibitors (simvastatin, lovastatin), leading to increased drug levels and rhabdomyolysis.[33] There is decreased metabolism of tacrolimus and indinavir as well.

Peripheral edema from an interaction between nifedipine and itraconazole has been reported.[34] The authors recommended that patients receiving azole antifungals and calcium channel blockers should be monitored for adverse effects, such as leg edema and hypotension, because of the increased serum concentration of the calcium channel blocker.

Fluconazole (and not itraconazole) interacts with losartan, an angiotensin II receptor antagonist hypertensive by inhibiting its metabolism to the active metabolite E-3174, possibly reducing the therapeutic effect.[35]

In contrast, with the triazole antifungals, terbinafine is an allylamine that does not inhibit CYP3A4.[32] This antifungal may be a viable therapeutic option in patients on concomitant therapy with drugs that can interact with triazole antifungals.

Allylamine Antifungals

Terbinafine is an orally active allylamine antifungal used in the treatment of dermatophytosis. At least seven CYP enzymes are involved in terbinafine metabolism. Recombinant human CYP predict that CYP2C9, CYP1A2 and CYP3A4 may be the most important for total metabolism.[36]

Reports suggest some degree of significant inhibition of CYP2D6 and CYP1A2 by terbinafine.[37] For now, terbinafine appears to be a potent inhibitor of CYP2D6, so clinicians should be aware of potential interactions. The area of greatest concern because of possible severity and common use would be bradycardia from excess β-blockade (e.g. propranolol) or from accumulation of donepezil.[38] Codeine can lose its analgesic effect because the active metabolite, morphine, is not formed when CYP2D6 activity is low.[39]

Azathioprine

Azathioprine is metabolized to 6-mercaptopurine (6-MP). There are three subsequent pathways for the metabolism of this metabolite. Both TPMT and xanthine oxidase metabolize 6-MP to inactive products, whereas hypoxanthine-guanine phosphoribosyltransferase (HGPRT) metabolizes 6-MP to active purine analogs, in particular 6-thioguanine. Allopurinol and febuxostat inhibit the metabolism of 6-MP via xanthine oxidase; this leads to increased levels of 6-MP and active purine analogs via HGPRT. The resultant effect is increased antimetabolite effects and associated toxicity.[40,41] Combining either azathioprine or 6-MP with allopurinol or febuxostat should be avoided. If latter must be used, an alternate immunosuppressant should be selected.

Colchicine

Colchicine is a substrate for PGP and concomitant use with PGP inhibitors has resulted in severe colchicine toxicity. It is also a substrate of CYP3A4 and inhibitors of this may also raise serum colchicine concentrations. As colchicine toxicity can be fatal, few situations would warrant the use of a PGP or CYP3A4 inhibitor with this drug. If such combination therapy must be used, monitor carefully for toxicity from colchicine, including diarrhea, abdominal pain, muscle pain, or weakness and paresthesias.[20] Discontinue both drugs immediately if toxicity is suspected.

Cyclosporine

Numerous drug interactions with CsA have surfaced associated with its metabolism and presystemic metabolism by the CYP3A4 enzyme and PGP in the liver and intestine, respectively. It is thought that GI tract metabolism may explain erratic absorption of CsA. In fact, CYP3A4 inhibitors have been administered intentionally to improve the bioavailability of CsA and reduce dosing requirements and the cost of administering this relatively expensive drug. Ketoconazole 200–400 mg daily can reduce the daily dose requirement of CsA by 60%–80%.[42] This combination is rarely used for the above rationale. Diltiazem reduces CsA dosing by as much as 30%,[43] while effects due to grapefruit juice have been variable. Other drugs that alter CsA concentrations via CYP3A4 inhibition include verapamil, nifedipine, fluconazole, itraconazole, ketoconazole, erythromycin, clarithromycin, and tacrolimus.[30] Nicardipine is also a CYP3A4 inhibitor. Conversely, CYP3A4 inducers, such as rifampin, phenytoin, carbamazepine, and phenobarbital, reduce CsA concentrations. Two

heart transplant patients receiving CsA developed acute rejection reactions after starting therapy with St. John's wort.[44] CsA trough levels, signs of toxicity and adequate immunosuppressive response should be monitored when these inhibitors or inducers are combined with CsA.

Grapefruit Juice

Grapefruit juice interactions are of potential clinical relevance in the individual patient for a wide range of drugs. Mechanism of interactions are exclusively pharmacokinetic, mediated by suppression of CYP3A4 and PGP in the small intestinal wall.[45] This results in a diminished first-pass metabolism with higher bioavailability and increased maximal plasma concentrations of substrate drugs for this enzyme and/or transporter. The effect is most pronounced in drugs with high first-pass degradation such as colchicine, felodipine, nifedipine, saquinavir, CsA, midazolam, triazolam, terazosin, ethinylestradiol, 17β-estradiol, prednisone, and the HMG-CoA reductase inhibitors lovastatin and simvastatin.[46,47] It is not yet clear which component in grapefruit juice is to blame. Bergamottin, a furocoumarin compound, is thought to be the major factor for this CYP3A4 enzyme inhibition.[48]

Even a change in the brand or batch of grapefruit juice may influence the grapefruit juice–drug interaction to an unpredictable degree, because grapefruit juice is a natural product that is not standardized in composition. Similar interactions have not been seen with other citrus fruit juices such as orange juice. Lack of 6,7-dihydroxybergamottin in orange juice probably accounts for the absence of CYP inhibitory effects.[49]

The idea of using grapefruit juice as a cost cutting measure has been used in patients on concomitant CsA therapy.[50] Because grapefruit juice inhibits the metabolism of CsA, combining the two would lower the required daily dose of CsA, thereby reducing drug costs. However, it has been difficult practically as grapefruit is not a standardized product.

It is recommended that patients refrain from ingesting grapefruit juice when taking a drug that is extensively metabolized by the CYP3A4 pathway, unless the absence of a potential interaction has been documented. Orange juice is a good alternative for such patients.

HMG-CoA Reductase Inhibitors

Although dermatologists may not prescribe these medications, their use by primary physicians and various specialists is widespread. Lovastatin and simvastatin undergo extensive (90% or more) presystemic metabolism by CYP3A4 in the gut wall and liver. Coadministration of itraconazole (or other potent CYP3A4 inhibitors) with lovastatin and simvastatin is contraindicated as they result in increased concentrations of the statin, resulting in rhabdomyolysis.[33,51–53] Atorvastatin is also metabolized by the hepatic CYP3A4 and hence may interact with CYP3A4 inhibitors.[54] Fluvastatin and rosuvastatin are metabolized via CYP2C9[55] and are therefore not likely to result in clinically significant drug interactions when used in combination with CYP3A4 inhibitors, but may interact with fluconazole and voriconazole. Pravastatin is not metabolized by CYP3A4[54] and thus may be a safe alternative.

Macrolide Antibiotics

Erythromycin and clarithromycin are inhibitors of CYP3A4, but azithromycin does not significantly inhibit CYP3A4.[56] When erythromycin is prescribed to a patient on long-term warfarin, there is a risk of increased plasma warfarin with increased anticoagulation and hemorrhage. This occurs because warfarin in relatively small quantities is a CYP3A4 substrate and erythromycin a potent inhibitor of this isoform. As for macrolides and statins used concomitantly, erythromycin and clarithromycin potentially increase the risk of statin-associated myopathy, whereas azithromycin does not. Erythromycin also interacts with sildenafil and carbamazepine, hence concurrent use should be avoided.[2]

Methotrexate

In patients who receive antineoplastic doses of methotrexate, ciprofloxacin, NSAID, penicillins and salicylates have been associated with methotrexate toxicity such as bone marrow suppression and GI toxicity. The mechanism of these interactions is via inhibition of anionic renal tubular secretion. The risk of the above interactions with low-dose methotrexate as is used for the treatment of psoriasis is probably much lower,[57] and indeed NSAIDs are often coprescribed for concomitant psoriatic arthritis. Nonetheless, one should be alert for methotrexate toxicity and, where possible, acetaminophen should be used to minimize risks of potential toxicity. Other drugs less likely to interact are ketoprofen, flurbiprofen and piroxicam.[58] Probenecid can increase methotrexate levels two to three fold by inhibiting renal tubular secretion.

Hormonal Contraceptives

Theoretically, antibiotics can reduce bacteria in the intestine that are involved in the enterohepatic

circulation of estrogens, leading to a reduction in estrogen serum concentrations. However, it has been reported that plasma levels are unchanged with several antibiotics.[59] Other potential mechanisms of drug-induced oral contraceptive failure include enzyme induction following rifampin, griseofulvin, phenytoin, oxcarbazepine, primidone and St. John's wort.[60]

Pimozide

Pimozide is a psychotropic drug with a narrow therapeutic index regarding neurologic and cardiac adverse effects. It is a recognized treatment for delusions of parasitosis. Pimozide alone can prolong the QT interval and it has been associated with arrhythmias such as torsades de pointes. Pimozide is oxidized by two CYP isoforms, CYP3A4 and CYP1A2, with the former being the responsible isoform at therapeutically relevant pimozide concentrations.[61] Although the contribution of CYP1A2 to pimozide metabolism appears marginal, this isoform may assume a greater role if the activity of CYP3A4 is very low. Therefore, a greater risk of adverse effects is expected when pimozide is prescribed simultaneously with various metabolic inhibitors of these two CYP pathways. These include the azole antifungals and macrolide antibiotics that are inhibitors of CYP3A4 and fluoroquinolones that inhibit CYP1A2.

There may be reduced efficacy of pimozide in the presence of inducers of CYP3A4, such as rifampin and carbamazepine and smokers may require higher pimozide doses because of higher CYP1A2 activity.

Pimozide is an inhibitor of CYP2D6 without being a substrate of this isoform. Identifying potential risk factors that could modulate the efficacy and toxicity of pimozide is important to optimize the safe use of this drug.

Warfarin

Warfarin is a drug with a very narrow therapeutic index, having a significant number of adverse drug interactions.[62] CYP2C9 is the enzyme primarily responsible for the metabolism of S-isomer of warfarin and CYP1A2 and CYP3A4 for the R-isomer. Infection and inflammation increase the production of cytokines that have been known to reduce the activity of CYP2C9. This change in warfarin response may occur during the time of antibiotic administration, but may be completely unrelated to the administration of the antibiotic. Drugs that inhibit the enzymes involved in the metabolism of warfarin may potentiate its effect.

For dermatologists who prescribe a new systemic therapy in the course of managing a patient on warfarin therapy, an additional INR should be obtained within 5–7 days of starting that new drug.

Herbal Remedies

Herbal medications are quite popular with the patients. They are considered to be "natural" and thus harmless. However, they can cause adverse effects and sometimes interact with medications. Dealing with herbal medications is a challenge, as the products are not standardized and often the patients do not know the ingredients of what they are taking. In a systematic review, ginkgo biloba, ginseng, milk thistle and echinacea were found to inhibit/induce the CYP enzymes, but the effect was generally weak at the doses commonly used.[63] Some herbal medications that may interact with prescription drugs are listed in Table 46.7.

Table 46.7: Herbal remedies that may interact with other drugs[2,63]

Herbal medication	Adverse effect	Interaction
Ginseng	Reduced efficacy of warfarin	Warfarin
Coenzyme Q10	Reduced efficacy of warfarin	Warfarin
Kava	CNS depressant	Alcohol, barbiturates, benzodiazepines, opiates
Licorice (*Glycyrrhiza glabralensis* or ura)	Contraindicated in hypertension, diabetes mellitus, hypokalemia, liver/kidney disorders	CsA, digoxin, prednisone, thiazides
Ginkgo (*Ginkgo biloba)*	Can cause spontaneous bleeding	Can potentiate aspirin, NSAID, warfarin, heparin
St. John's wort	Reduced CsA levels; reduced efficacy of oral contraceptives	CsA, oral contraceptive

CsA - cyclosporine A;
NSAID - nonsteroidal anti-inflammatory drug.

PHARMACODYNAMIC REACTIONS

Pharmacodynamic interactions can occur from an antagonistic or synergistic drug effect. The synergistic effects can occur with the therapeutic or adverse effects of the drug.

Antagonistic Effect

Interactions through antagonistic effects can occur when two drugs used in an individual patient have opposing end-organ results. Antagonistic effects can arise when a patient taking a β-blocker develops anaphylaxis and may be refractory to the therapeutic effects of epinephrine. A recent meta-analysis of randomized controlled trials studied the efficacy of folic acid and folinic acid in reducing methotrexate-induced GI toxicity in patients with rheumatoid arthritis.[64] This review shows a reduction of 80% in mucosal and GI adverse effects in patients receiving low-dose (5 mg weekly) folic acid. On the flip side, there are no indications so far that folic acid may alter the efficacy of methotrexate. No major differences in disease activity between placebo and folic acid at low or high dosages were found. When prescribing antagonistic medications, one must realize the potential for reduced efficacy of the intended medication.

Synergistic Effects

Interactions through synergistic effects can occur when two drugs used in an individual patient share the same target organ for toxicity. When methotrexate and sulfonamides are coprescribed, methotrexate may induce folate deficiency-related, sulfonamide-induced, megaloblastic anemia.[65] Preliminary evidence suggests that the risk of gastric ulcers with combined use of alendronate and naproxen is substantially greater than with the use of either drug alone.[66]

LEARNING ESSENTIALS

- Commonly used drugs in dermatology are potential causes of drug interactions, e.g. ketoconazole, itraconazole, antibiotics, and methotrexate.
- Majority of drug reactions are caused by a small number of drugs; 80:20 rule, i.e. 20% of drugs cause 80% of the reactions.
- A good drug history including over-the-counter drugs and herbal medications is important.
- Knowledge of genetic polymorphisms may help in identifying individuals susceptible to drug interactions. Doing these tests, where available may prevent adverse events.
- Vigilance is important in preventing serious adverse drug interactions. Elderly patients, patients with comorbidities, and patients taking multiple drugs should particularly be paid more attention to, when prescribing new medications.

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Chapter

47

Multiple Drug Hypersensitivity Syndrome and Multiple Drug Intolerance

Sarita Sasidharanpillai

SUMMARY

Multiple drug allergy syndrome (MDS) refers to drug allergies to two or more chemically and pharmacologically different drugs. It is a relatively underrecognized entity. With better understanding of the immunological mechanisms underlying the adverse drug reactions, it is realized that data pertaining to MDS in literature comprised heterogeneous entities such as pseudo allergic states [e.g. nonsteroidal anti-inflammatory drug (NSAID) intolerance] and multiple drug intolerance syndrome (MDIS) besides true hypersensitivity reactions. The current concept is that multiple drug hypersensitivity syndrome (MDHS) is a better terminology to describe allergic reactions to two or more chemically and pharmacologically unrelated drugs where the diagnosis of hypersensitivity is confirmed by appropriate drug allergy workup. Patients with drug hypersensitivity in the past, particularly severe reactions such as drug reaction with eosinophilia and systemic symptoms (DRESS) are more likely to exhibit MDHS.

INTRODUCTION

In 1966, Smith et al. identified history of prior allergic reaction to a drug as a risk factor for penicillin allergy.[1] Since then several authors have documented patients manifesting adverse reactions to multiple unrelated drugs.[2,3] On most occasions, diagnosis was based on history alone and often the culprit drugs were antibiotics, even though other drug groups were occasionally reported as potential offenders. This was described as a separate entity "multiple drug allergy syndrome" by Sullivan et al. in 1989 and was defined as drug allergies to two or more chemically and pharmacologically different drugs, mostly antibiotics.[3] It is clearly different from *cross reactivity* (that arises due to structural similarities, common metabolic pathways, or pharmacological mechanisms shared by culprit drugs) and flare-up reactions. *Flare-up reaction* is the exacerbation of an existing drug hypersensitivity by introduction of a new unrelated drug when the patient is in the acute stage of initial drug reaction. It is attributed to the immune activation induced by the first reaction rendering the patient susceptible to adverse reaction to a second drug introduced during the heightened state of immune activity. The patient may tolerate the second drug once this milieu of immune activation subsides.[4,5]

Earlier studies documented urticaria and angioedema as the most common presentations of multiple drug allergy syndrome.[6] Later, it was realized that patients with multiple drug allergy manifested different reaction patterns, including maculopapular rash, fixed drug eruption, Stevens–Johnson syndrome/toxic epidermal necrolysis spectrum of illness, anaphylaxis, serum sickness–like reaction, and immune cytopenias.[4,5]

With advances in the understanding of complex immunological mechanisms involved in adverse drug reactions and with the introduction of in vivo and in vitro tests to determine the offending drug, it was recognized that many cases branded as multiple drug allergy syndrome showed negative results on prick, intradermal and patch skin tests; lymphocyte transformation test and specific antibody determination test. A significant percentage of those who yielded negative reports on drug allergy workup experienced pseudo allergic reactions.[4–6]

Pseudo allergic reactions are clinically indistinguishable from drug hypersensitivity reactions and often closely mimic immediate-type, immunoglobulin E (IgE)-mediated reactions, but are not associated with the production of antibodies or sensitized T cells.

Here, drug through its chemistry or pharmacology directly activates or stimulates the release of inflammatory mediators such as histamine, prostaglandins, leukotrienes, or kinins. Common drugs associated with pseudo allergic reactions are nonsteroidal anti-inflammatory drugs (NSAIDs), narcotics, and angiotensin-converting enzyme inhibitors.[4–8]

IgE/T-cell-mediated mechanism was considered unlikely in patients with multiple NSAID intolerance because these patients showed adverse reaction to structurally unrelated NSAIDs and further evaluation ruled out an immunological basis in most of these cases. It is recognized that these reactions are mainly associated with cyclooxygenase 1 (COX-1)-inhibiting drugs and those drugs with little effect on the COX-1 enzyme (i.e, COX-2 inhibitors) are generally well tolerated suggesting a central role for COX-1 inhibition in NSAID-induced immediate pseudo allergic reactions. COX inhibition shifts arachidonic acid metabolism toward the 5-lipoxygenase pathway, leading to production of cysteinyl leukotrienes (LTC_4, LTD_4, LTE_4) that are hundred times more potent than histamine in inducing wheal-and-flare reactions.[7,8]

In 2005, Jex-Collet et al. established that skin and in vitro tests can help in confirming multiple drug hypersensitivity.[9] *The current concept* is that the term *"multiple drug hypersensitivity syndrome (MDHS)"* would be a better terminology to denote immune-mediated sensitization to multiple drugs and should be reserved to describe adverse reactions to two or more chemically unrelated drugs where the diagnosis of hypersensitivity drug reaction is confirmed by appropriate drug allergy workup.[4]

Another entity that has to be clearly distinguished from MDHS is *"multiple drug intolerance syndrome (MDIS)."*

MDIS is defined as the manifestation of various adverse reactions to three or more chemically, pharmacologically, and immunogenically unrelated drugs taken independently with negative results in skin tests and specific IgE measurements to the suspected drugs. It usually is a self-reported subjective entity, shows a clear female predilection, and has a marked psychosomatic component. It differs from MDHS in terms of its non-immunogenic basis.[4,10,11]

The major hurdle in understanding more about MDHS is the scarcity of data. Moreover, in literature this term has been used to indicate heterogeneous conditions.[5] The ethical concerns in opting for in vivo tests in severe drug reactions and the lack of access to in vitro tests in many centers have added to the confusion.

EPIDEMIOLOGY

Multiple Drug Hypersensitivity Syndrome

According to various studies, 0.6%–12.6% of patients reporting with suspected drug allergy have MDHS.[4,9,12] As per the literature, majority of patients with MDHS show hypersensitivity to different classes of antibiotics followed by patients showing hypersensitivity to both antibiotics and NSAIDs.[4,12] But more recent data suggest that multiple antibiotic sensitivity is not as frequent as suggested by earlier studies.[12] The common cutaneous manifestations cited as features of adverse reactions to antibiotic therapy are maculopapular and urticarial eruptions. This, when taken into consideration with the fact that most often antibiotics are prescribed for a febrile infective illness (probably viral), indicates that at least some of the cases described as due to antibiotic allergy in earlier studies (where diagnosis was based on history and clinical features alone without immunological workup) could be infective exanthema. In addition, in some instances underlying viral infection through immune stimulation might have rendered the patient susceptible to a transient allergic reaction to a particular drug during the period of illness.[12]

Female sex, allergy to NSAID, human immunodeficiency virus infection, systemic lupus erythematosus, and history of one severe drug reaction [especially drug reaction with eosinophilia and systemic symptoms (DRESS)] are the risk factors identified in MDHS.[4,5,13,14] In one series of patients with MDHS, the autoimmune associations noted were Hashimoto's thyroiditis, Graves' disease, Sjögren's syndrome, systemic lupus erythematosus, and rheumatoid arthritis.[15]

Multiple Drug Intolerance Syndrome

Approximately 2% of those taking medicines and nearly 5% of those with history of adverse reactions to medications are known to have MDIS.[10,11] According to different studies, the common offending drugs reported to induce adverse reactions among patients with MDIS are antibiotics, narcotics, and NSAIDs.[10,11] Two large population–based studies recognized female sex (one study reported obese females), polypharmacy, previous hospitalization, and anxious personality as risk factors for MDIS.[10,11]

PATHOGENESIS

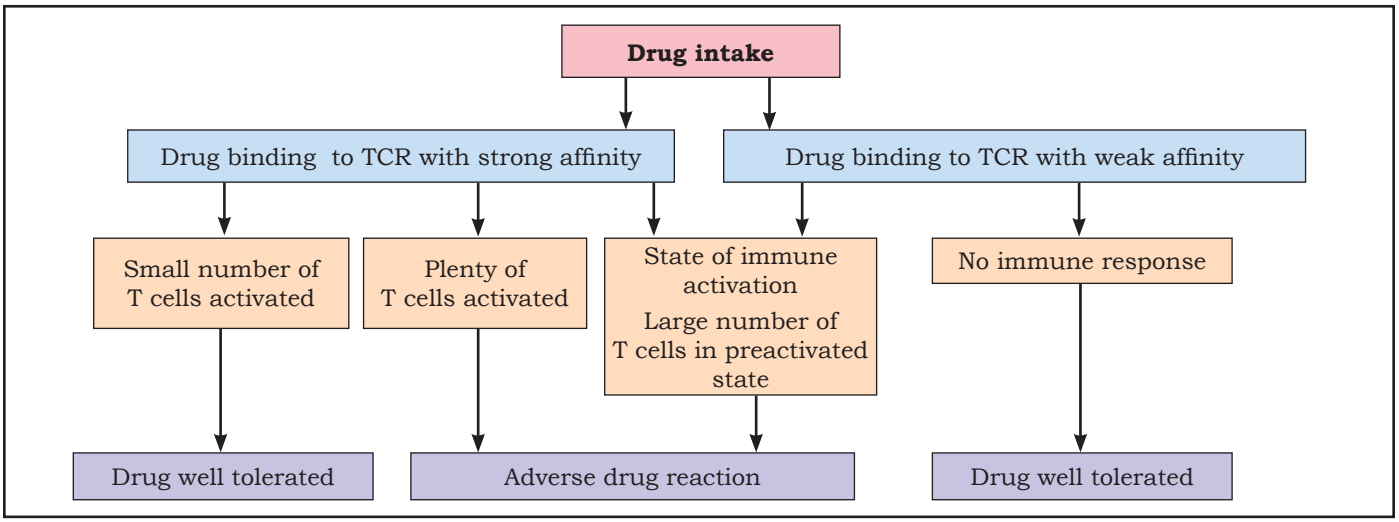
Multiple Drug Hypersensitivity Syndrome

The exact pathogenesis of MDHS is not clearly understood. In vitro drug-induced interferon γ (IFNγ) release towards multiple unrelated drugs has been demonstrated in cases with MDHS indicating a role

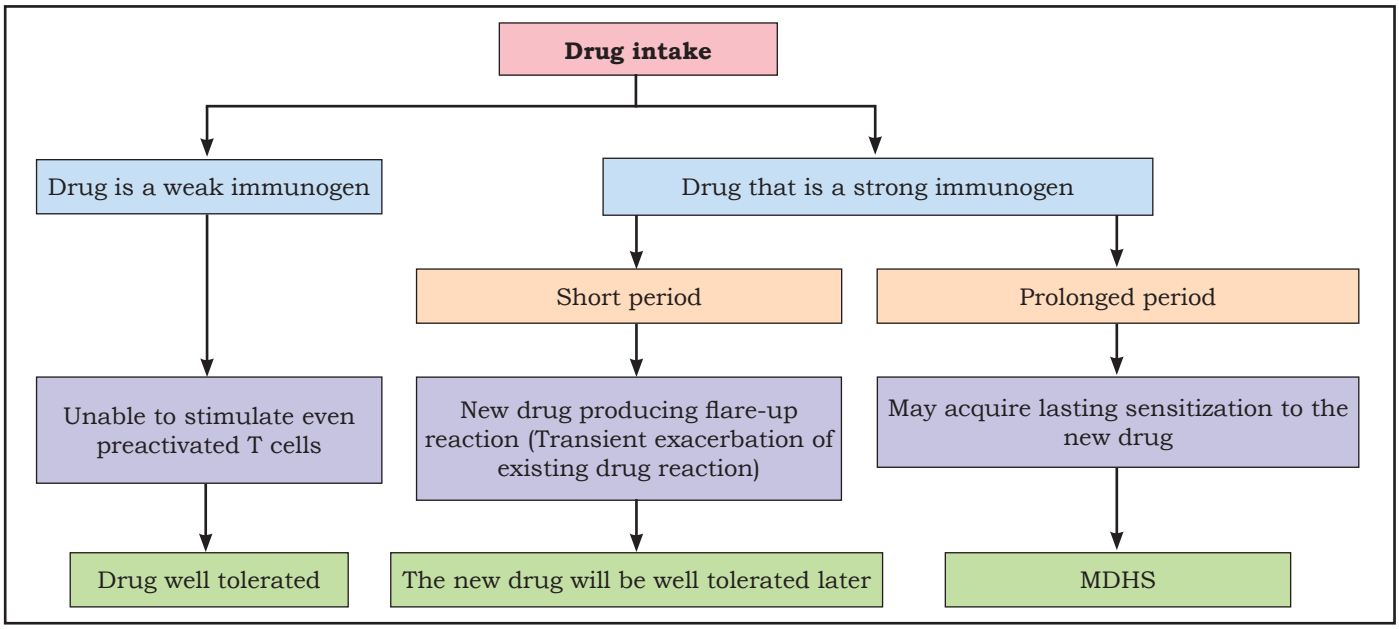
for T cells. It is further suggested that drug-induced IFN-γ release could serve as a useful tool to diagnose MDHS.[16]

Another proposed theory that has found much acceptance is the role played by a severe drug reaction in precipitating MDHS.[4,5] It is reported that up to 10% of patients with severe and well-documented immune-mediated drug hypersensitivity are at risk for developing MDHS.[9,17] According to pi model, it is stated that the potential of a drug to precipitate T cell-mediated adverse reaction depends on the affinity with which the drug binds to the T cell receptor and also on the readiness of the T cells to react (Flowchart 47.1).[5] When the immune system is in an activated state (as in case of a severe drug hypersensitivity reaction or concomitant viral infection), even a weak drug/T cell interaction can result in adequate T cell stimulation to produce an immune response, whereas even a strong drug/T cell receptor interaction may fail to elicit a response, if only small number of T cells are activated.[5]

As far as the sensitization to a drug introduced during the acute stage of a severe drug reaction or viral infection is concerned, it may have three future courses that are depicted in Flowchart 47.2.[5,12]



Flowchart 47.1: Pathogenesis of multiple drug hypersensitivity syndrome (MDHS): Drug/T cell interaction is crucial in the outcome of MDHS. The possibility of ADR developing is dependent on the affinity with which the drug binds and the quantum of T cells activated. (TCR - T cell receptor).



Flowchart 47.2: Possible outcomes in a patient when a new drug is ingested during state of immune activation induced by severe drug reaction or viral infection. (MDHS - multiple drug hypersensitivity syndrome)

In a prospective study on the efficacy of patch testing in identifying sensitization to multiple drugs, it was reported that 18% of patients with DRESS developed sensitization to multiple drugs given simultaneously during DRESS. Similar statistics for acute generalized exanthematous pustulosis and Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) were 6.6% and 5.8%, respectively.[15] None of these patients had any history of drug reaction prior to the described severe drug reaction, thus underscoring the theory of concomitant sensitization.[18]

Several theories are postulated to explain the occurrence of MDHS following severe drug reaction. In their study on DRESS, Takahashi and coworkers noted an expansion of regulatory T cells in serum during the acute stage of DRESS. Following resolution of DRESS, the expanded T cell population returns to normal levels but becomes functionally impaired, which is cited as a reason for autoimmune manifestations following DRESS. This defective regulatory T cell population is proposed to play a role in loss of tolerance to other antigens including unrelated drug molecules. It is suggested that immune reaction to a drug should be seen as failure of body's tolerance; hence, any patient with history of drug allergy is prone to develop immune-mediated adverse reactions to other drugs, as well as autoimmunity.[19]

Contrary to the findings of Takahashi and coworkers, Daubner et al. did not find any evidence of defective regulatory T cell function in patients with MDHS. They found that the drug-reactive T cells from patients with MDHS belonged to an in vivo preactivated T cell fraction (CD4+ $CD25^{dim}$ T cell fraction) whereas those from patients with allergy to a single drug belonged to the resting CD4+ $CD25^{neg}$ T cell fraction.[20]

This preactivation in patients with MDHS seems to persist for several years, and the reason for this prolonged preactivation status even when drug exposure has ceased remains obscure. One possible explanation is the endogenous herpesviruses induced in vivo T cell activation. Herpesviruses are known to stimulate circulating CD4+ and CD8+ T cells inducing a phenotype similar to the activated T cell fraction of patients with MDHS. It is supported by the observation of initial drug reaction in many patients with MDHS being DRESS or other severe drug reactions associated with massive herpesvirus reactivations (human herpesvirus 6 and 7, cytomegalovirus, and Epstein–Barr virus). Future studies are needed to confirm or refute this hypothesis.[20]

Multiple Drug Intolerance Syndrome

Probable role for nonspecific histamine release by mast cells and basophils has been advocated as a pathogenic mechanism for MDIS. The positive response to autologous serum skin test observed in patients with MDIS points to a role for autoreactive antibodies that when triggered by certain drugs act on the high-affinity IgE receptor (FceRI) resulting in histamine release. More data are needed to consider this as the underlying pathogenesis in MDIS.[6,21]

Available data predict a role for psychological factors in MDIS. It has been pointed out that anxious patients with increased likelihood of somatization are more likely to present with MDIS. This is explained on the basis of nocebo effect, which is defined as the appearance of negative effects on exposure to a non-harmful substance. It is believed that patients with history of a drug reaction are more likely to harbor negative thoughts associated with drugs, which can manifest as subjective symptoms. The clinician may find it difficult to distinguish between symptoms of somatization and those due to drug allergies.[8,22] The nonspecific symptoms observed in patients reporting with allergy to multiple unrelated drugs in one Indian study were dizziness, weakness, itching, headache, nausea, vomiting, abdominal pain, and tightness of the chest.[23]

CLINICAL MANIFESTATIONS

Multiple Drug Hypersensitivity Syndrome

MDHS is broadly classified into two types. It can develop to different drugs administered simultaneously or sequentially (developing hypersensitivity to different drugs at different times, sometimes years apart) (Table 47.1).[4,5] MDHS can manifest as both immediate and nonimmediate reactions. Immediate allergic reactions are thought to be IgE mediated and usually appear within an hour of the last drug administration. Clinical patterns are urticaria, angioedema, rhinitis, bronchospasm, and anaphylactic shock.[4,5,12,24–27]

Nonimmediate reactions manifest later than 1 hour after the last drug administration. Maculopapular rash, delayed-appearing urticarial rash, SJS/TEN spectrum of illness, fixed drug eruption, and DRESS belong to this group and are T cell mediated.[12,24–27]

One patient can present with different reaction patterns to different drugs. A patient can develop an IgE-mediated reaction to one drug and can manifest a T cell-mediated reaction to another drug another time, but IgE and T cell-mediated reactions are usually not reported together.[5]

Multiple Drug Intolerance Syndrome

The most common manifestations of MDIS are urticaria and angioedema.[28] Very severe drug reactions

Table 47.1 Comparing the clinical characteristics of MDHS and MDIS[4,5,10,11]

S. No.	Demography	MDHS	MDIS
1	Definition	Adverse reactions to two or more chemically unrelated drugs where the diagnosis of hypersensitivity drug reaction is confirmed by appropriate drug allergy workup.	Various adverse reactions to three or more chemically, pharmacologically, and immunogenically unrelated drugs; taken independently with negative results in skin tests and specific IgE measurements to the suspected drugs.
2	Common age group	Adults	Elderly on multiple drugs
3	Sex predilection	Females	Marked female predilection
4	Common drugs	Antibiotics, NSAIDs, anticonvulsants	Antibiotics, narcotics, NSAIDs
5	Risk factors	Female sex, adverse reaction to NSAID, SLE, HIV infection, history of severe drug reaction	Female sex, polypharmacy, previous hospitalization, anxious personality
6	Common reaction patterns	Both IgE-mediated and T-cell-mediated reaction patterns seen; same patient can manifest different reactions at different times.	Urticaria and angioedema; severe reactions less likely.

MDHS - multiple drug hypersensitivity syndrome; MDIS - multiple drug intolerance syndrome; NSAIDs - nonsteroidal anti-inflammatory drugs; SLE - systemic lupus erythematosus; HIV - human immunodeficiency virus.

are rarely seen in MDIS consistent with its nonallergic pathogenesis. In a series of 480 patients with MDIS, only 4 manifested SJS, there were 3 occurrences of nonallergic anaphylactic shock, and none of the study subjects developed TEN or DRESS.[28]

Differential Diagnosis

MDHS needs to be differentiated from cross reactivity, flare-up reactions, and MDIS. Ramam et al. in a study documented that most of the patients who presented with history of allergy to multiple drugs were able to tolerate the same and alternate drugs when rechallenged.[23] This supports the fact that on most occasions when the cofactors (such as viral infection or a serious drug reaction in acute stage) that induce immune stimulation are not there, patients may tolerate the drugs towards which they showed sensitization earlier.[5,12]

An in-depth knowledge regarding the chemical structure and pharmacological mechanisms of drugs may help one from misdiagnosing cross reactivity as MDHS. Proper drug allergy workup will help to distinguish MDHS from MDIS (Flow charts 47.3 and 47.4).

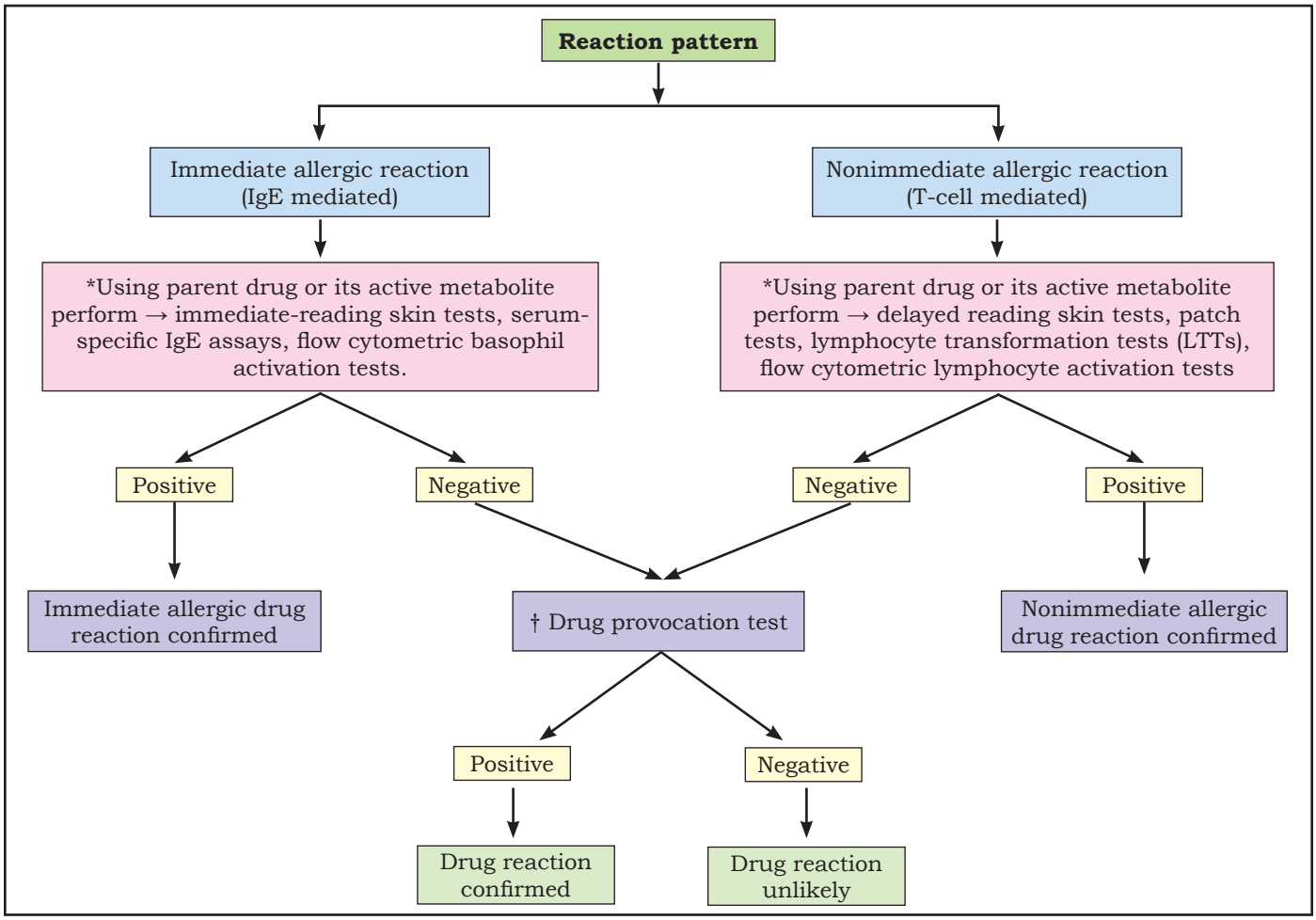
Management

Multiple Drug Hypersensitivity Syndrome

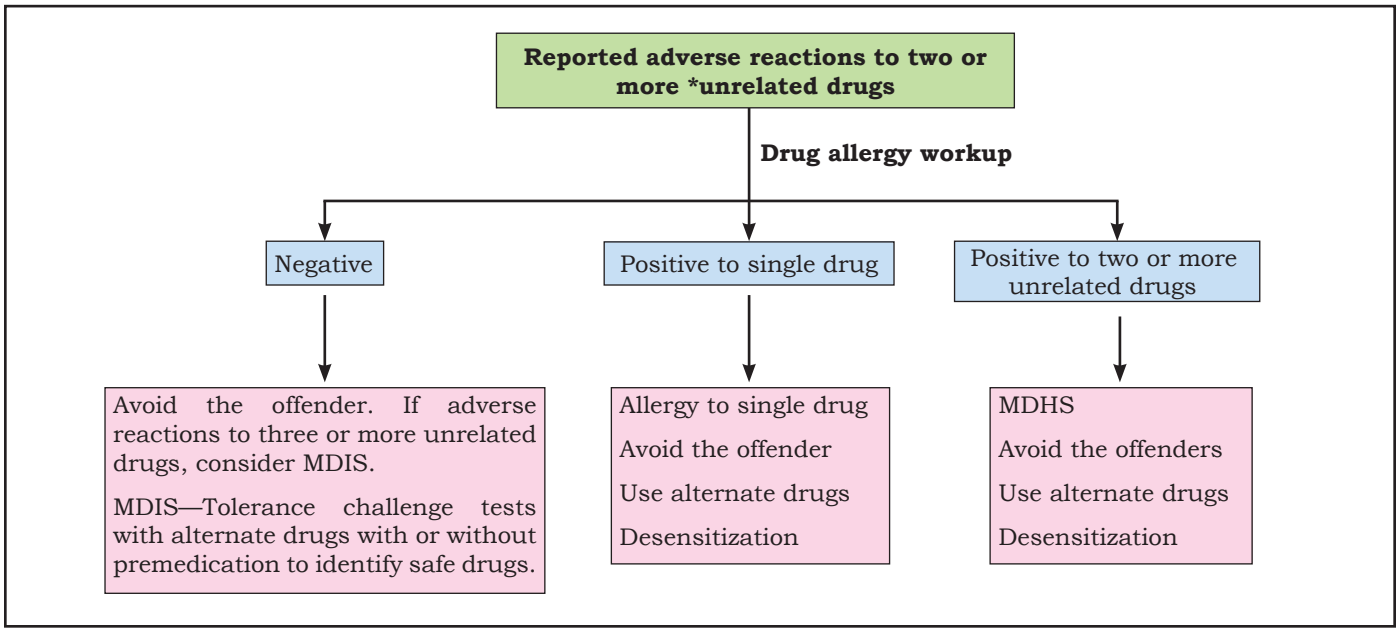
Appropriate drug allergy workup forms the cornerstone of diagnosis and management of MDHS (Flowchart 47.4).[5,12] The choice of immunological tests to be performed depends on the type of allergic reaction manifested by the patient to a particular drug (Flowchart 47.3).[12,24–27]

The sensitivity of the skin and in vitro tests is not 100% in determining the offending drug. One such instance is when the adverse reaction is caused by the drug metabolite rather than the parent compound. In such cases, it is essential to use the active metabolite in the diagnostic tests so as to avoid getting false negative results.[12] At times, drug provocation tests may be necessary to identify the offending drug, since the skin tests and in vitro tests have low negative predictive value. But drug provocation is absolutely contraindicated in severe drug reactions.[12,24–27.]

Management strategy of MDHS is comparable to that of single-drug allergy (Flowchart 47.4). On most occasions, it is possible to find an alternate medicine that is chemically and pharmacologically unrelated; but in situations requiring the same drug that provoked a reaction (without any alternate option) as a lifesaving measure, patient may be advised to undergo desensitization under critical care setting. Desensitization is appropriate only for IgE-mediated drug reactions and not recommended for severe drug reactions such as SJS/TEN.[4,5,12,28,29]



Flowchart 47.3: Drug allergy workup.[12,24–27]
(*Prick tests and intradermal tests are the common skin tests used to evaluate drug allergy. Post test readings are taken after 20 minutes in immediate-type allergic reactions whereas in nonimmediate reactions readings are taken after 48 and 72 hours.[10,20,21–23] †Drug provocation test is absolutely contraindicated in severe drug reactions.)



Flowchart 47.4: Management of patients reporting with adverse reactions to multiple unrelated drugs. (MDIS - multiple drug intolerance syndrome; MDHS - multiple drug hypersensitivity syndrome.)

Multiple Drug Intolerance Syndrome

Management of patients with MDIS is a difficult task because patients are anxious and believe they may develop adverse reactions to any drug. Clinicians also wary on handling such patients, often withholding necessary treatment. The first step in managing these patients is by taking detailed history and listing the drugs that produced adverse reactions in the past. Proper drug allergy workup will help to differentiate this from MDHS.

Higher prevalence of MDIS in elderly women on multiple medicines indicates a role for polypharmacy. Unnecessary drugs, if any, may be stopped in the affected. Patient should avoid drugs precipitating adverse reactions. Commonly required drugs that could be safely used in those with MDIS could be determined by performing tolerance challenge tests with or without premedication using drugs unrelated to known offending agents.

When choosing alternative drugs, care should be taken to avoid those belonging to the same families or those sharing the same metabolism or pharmacological action as those which had produced symptoms in the past. It is recommended to initiate the tolerance challenge tests with 1/10 of the therapeutic dose followed by 2/10, 3/10, and 4/10 of the therapeutic dose every 30 minutes up to the total therapeutic dose or appearance of symptoms under critical care setting. Patients should be monitored throughout testing and for 1 day after testing. All patients are advised to undergo a single-blind challenge test with placebo before the tolerance challenge test.[28]

Patients with history of mild adverse reactions are not advised any premedication before tolerance challenge test. Those who experienced moderate symptoms that needed treatment with oral antihistamines or corticosteroids or both are prescribed premedication with 500 mg sodium cromolyn, per orally, 30 minutes before the test. Oral antihistamines such as cetirizine or loratadine 10 mg is administered 30 minutes before tolerance challenge test in those undergoing parenteral challenge tests or those who had had severe reactions in the past that needed treatment with parenteral antihistamines or corticosteroids. In most patients, through tolerance challenge tests, an alternate drug that can be safely used could be identified. In some cases who develop adverse reactions on tolerance challenge test, a different premedication can ensure tolerance. In the small number of patients who continue to develop symptoms despite trying different premedications, the test may be repeated with another drug to find a safe option. Identifying drugs that can be used safely for commonly prescribed diseases can offer great relief to the patient and treating clinician.[28]

Judicious selection of drugs for tolerance challenge test goes a long way in identifying the safe drugs. For patients with intolerance to NSAIDs such as aspirin and pyrazolones, preferred drugs for tolerance challenge tests are nimesulide and acetaminophen. Aspirin and pyrazolone are inhibitors of COX-1 and COX-2, whereas nimesulide and acetaminophen are poor inhibitors of COX. In patients with history of adverse reactions to paracetamol, a better option for tolerance challenge test will be selective COX-2 inhibitors and noninhibitors of COX.[28]

SUMMARY

MDHS exists as a separate entity. It is over diagnosed on occasions when diagnosis is made on the basis of history alone. It can be under diagnosed as well since skin tests and in vitro drug tests are not 100% accurate; moreover, most centers lack facility for in vitro drug tests. All these have created obstacles in learning more about this condition and designing a protocol for managing patients.

With newer and newer drugs being introduced on a daily basis, MDHS should be a top priority of research. Multicenter studies on different population groups with proper immunology workup may help us to answer the queries posed by these hypersensitivity drug reactions.

LEARNING ESSENTIALS

- MDHS exists as a separate entity. Multiple drug hypersensitivity syndrome (MDHS) is defined as drug allergies to two or more chemically and pharmacologically different drugs. It has to be distinguished from multiple drug intolerance syndrome (MDIS) which is non-immunologic unlike MDHS.
- Avoiding drugs (and related medications) identified as offenders through proper drug allergy workup is the recommended approach in MDHS.
- Avoiding drugs provoking adverse reactions and determining safe alternate options through tolerance challenge tests is the advocated strategy in MDIS.

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Chapter

48

Desensitization Principles in Cutaneous Adverse Drug Reactions

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SUMMARY

Drug hypersensitivity accounts for more than 15% of all adverse drug reactions. They are unpredictable in nature, can affect any organ or system, and range widely in severity from mild pruritus to anaphylaxis. Although in most cases, the suspected drug is to be avoided in future, there are certain conditions where the particular drug is essential for optimal therapy. It is in these circumstances that desensitization is of relevance. For immediate type of hypersensitivity reactions, there are multiple rapid desensitization protocols that are well studied and established as safe; however, desensitization is not generally advocated in severe cutaneous reactions. This chapter discusses desensitization and reintroduction principles and protocols in hypersensitivity drug reactions.

INTRODUCTION

Drug hypersensitivity accounts for more than 15% of all adverse drug reactions.[1,2] They are unpredictable in nature, can affect any organ or system, and range widely in severity from mild pruritus to anaphylaxis. The World Allergy Organization recommends categorizing hypersensitivity reaction (HSRs) on the basis of the timing of the appearance of symptoms as *immediate* which develops within 1 hour of drug exposure or *delayed-type* i.e. onset after 1 hour of drug exposure.[3] Although in most cases, the suspected drug is to be avoided in future, there are certain conditions where the particular drug is essential for optimal therapy. It is in these circumstances that desensitization is relevant.

Desensitization is defined as the induction of a temporary state of tolerance of a compound responsible for a HSR. It is performed by administering increasing doses of the suspected medication over a short period of time, from several hours to a few days, until the total cumulative therapeutic dose is achieved and tolerated. On discontinuing the drug, this tolerance is lost within a period varying from a few hours to a few days.

Through rapid desensitization, patients with immediate HSRs (IgE and non-IgE dependent) can safely be administered important medications while minimizing or completely inhibiting adverse reactions. Typically, rapid desensitization procedures are used for administering antibiotics such as penicillins, cephalosporin, chemotherapeutic agents, and monoclonal antibodies safely.

Successful desensitization has also been documented in delayed drug HSRs such as sulfonamide hypersensitivity in HIV-positive patients or hypersensitivity to antibiotics in patients with cystic fibrosis.

HYPERSENSITIVITY REACTIONS

Gel and Coombs delineate HSRs into four types namely type I immediate HSR, type II antibody-mediated (cytotoxic) HSR, type III immune complex–mediated HSR, and type IV delayed-type HSR. Immediate HSRs are usually IgE mediated (true allergies) and involve antigen binding to mast cell/basophil surface receptors, but in certain cases, an alternative mechanism may be responsible. Non-IgE-mediated reactions, also known as pseudo allergic or histamine release reactions, can have manifestations similar to true allergic reactions. These are dose dependent and associated with drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), radiocontrast agents, and vancomycin ("red man syndrome"), which directly stimulates the degranulation of mast cells and basophils.[4–6]

Typically, type I HSR can involve cutaneous, respiratory, cardiovascular and gastrointestinal systems (Table 48.1). Less common signs and symptoms include neuromuscular symptoms, such as visual changes, pain (back, chest, and pelvis), numbness/weakness or in some cases fever and chills.[7]

Table 48.1: Manifestations of type I hypersensitivity reaction

Cutaneous	Respiratory	Cardiovascular	Gastro-intestinal
Flushing	Sneezing	Chest pain	Nausea
Pruritus	Nasal congestion	Tachycardia	Vomiting
Urticaria	Dyspnea	Sense of impending doom	Diarrhea
Angioedema	Wheezing	Presyncope	Abdominal pain
	Coughing	Syncope	
	Hypoxia	Hypotension	
	Throat tightness		

Assessment of severity of reactions is pertinent for management. Type I HSR is categorized into mild, moderate, and severe on the basis of severity (Fig. 48.1). Desensitization is used for moderate-to-severe HSR.

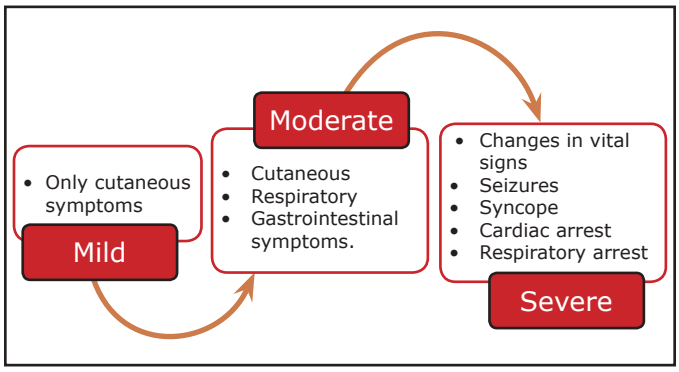

Fig. 48.1: Categorization of type I hyper sensitivity reaction (HSR).

Most cutaneous adverse drug reactions (CADRs) occur as delayed-type reactions (Gels and Combs type II, III, and IV), presenting as rashes or skin lesions with varied morphology and patterns. The predominant findings in type IV HSRs typically involve the skin. There are several commonly recognized patterns of cutaneous involvement that can occur: contact dermatitis, morbilliform eruptions, Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug-induced hypersensitivity syndrome (DIHS). Few definitions related to drug desensitization are the following:[8]

- *Drug allergy* is defined as an immunologically mediated response to a pharmaceutical and/or formulation (excipient) agent in a sensitized person.
- *Drug intolerance* is an undesirable pharmacologic effect that may occur at low or usual doses of the drug without underlying abnormalities of metabolism, excretion, or bioavailability of the drug. Humoral or cellular immune mechanisms are not thought to be involved, and a scientific explanation for such exaggerated responses has not been established.
- *Drug tolerance* is defined as a state in which a patient with a drug allergy will tolerate a drug without an adverse reaction. Drug tolerance does not indicate either a permanent state of tolerance or that the mechanism involved was immunological.
- *Induction of drug tolerance*, which has often been referred to as drug desensitization, is more appropriately described as a temporary induction of drug tolerance. Induction of drug tolerance can involve IgE immune mechanisms, non-IgE immune mechanisms, pharmacologic mechanisms, and undefined mechanisms. All procedures to induce drug tolerance involve administration of incremental doses of the drug.
- *Drug desensitization* is one form of induction of immune drug tolerance by which effector cells are rendered less reactive or nonreactive to IgE-mediated immune responses by rapid administration of incremental doses of an allergenic substance.
- *Graded challenge* or test dosing describes administration of progressively increasing doses of a medication until a full dose is reached. The intention of a graded challenge is to verify that a patient will not experience an immediate adverse reaction to a given drug. The medication is introduced in a controlled manner to a patient who has a low likelihood of reacting to it. Unlike procedures that induce drug tolerance, graded challenges usually involve fewer doses, are of shorter duration, and are not intended to induce drug tolerance. Several other terms such as reintroduction and rechallenge procedures have been used for this purpose by various workers in various ways.

PRINCIPLE AND MECHANISM OF DESENSITIZATION

Rapid drug desensitization (RDD) is a process by which mast cells are rendered hyporesponsive to a medication allergen by providing temporary tolerance

in drug hypersensitive patients, protecting them from anaphylaxis. The proposed mechanisms[9] through which rapid desensitization works include.

- Depletion of activating signal transduction components such as SYK (Spleen tyrosine kinase).
- Subthreshold depletion of mediators.
- Internalization of FCeRI through progressive cross-linking at a low antigen concentration.

INDICATIONS

Desensitization is largely safe and effective for IgE-mediated drug allergy. Indications and criteria for performing desensitization[10] are as follows:

1. The urgent need for therapy or prophylaxis of a disease.
2. The drug concerned is irreplaceable or more effective than the potential alternatives.
3. The non-availability of a non-cross-reacting pharmaceutical agent for treatment.
4. The previous delayed drug reaction was not severe or life-threatening.
5. The potential benefit outweighs the potential risks.

CONTRAINDICATIONS

Contraindications to drug desensitization procedure are listed in Table 48.2. They can be absolute or relative, where it can be undertaken after careful individual risk/benefit assessment.[11]

TESTS FOR DETERMINING HYPERSENSITIVITY

The diagnostic evaluation of type I HSR involves in vivo and in vitro tests. In vivo tests include cutaneous testing [skin prick test(SPT) and intradermal test (IDT)][12] and drug provocation test (DPT).[13-16] In vitro tests include specific IgE testing by radioallergosorbent testing (RAST), enzyme-linked immunosorbent assay (ELISA) or fluoroenzyme immunoassay (FEIA)[17] and basophil activation testing.[18] The combination of in vivo tests, such as SPT and IDT and oral challenge, is generally considered as the gold standard for diagnostic testing of immediate drug allergy.

PROCEDURE AND PROTOCOLS

Desensitization in Immediate Drug HSRs

Though not unique or of much concern to dermatology practice, these procedures have been developed as standardized methods for antibiotics and chemotherapeutic agents. A thorough individual risk–benefit evaluation is explained to the patient, and confident dialogue between the patient and doctor with respect to the medical condition and its treatment has to be performed, and the benefits must outweigh the risks. Caution and surveillance are mandatory in all cases. Desensitization is associated with the risk of acute HSRs and should be performed in an adequately controlled setting under the supervision of a well-trained physician who is familiar with the procedures and treatment of anaphylaxis. An intravenous line and continuous monitoring are obligatory. When feasible, it must be performed in an intensive care unit, however, if not so, it should always be done only in an indoor setup under close observation and by an experienced and confident physician. Initial rapid desensitization should only be performed in settings with one-on-one nurse–patient care and where resuscitation personnel and resources are readily available. Equipments for treating allergic reactions and for cardiopulmonary resuscitation must be accessible and should include all drugs necessary to treat anaphylaxis.[10]

Table 48.2: Absolute and relative contraindications of desensitization

Absolute	Relative
Severe or life-threatening drug-induced diseases such as SJS/TEN, DHS/DIHS/DRESS	AGEP
Cutaneous or systemic vasculitis	Underlying autoimmune disorders
Drug-induced autoimmune disorders	Severe cardiac disease/hemodynamically unstable patient
Drug-induced severe general symptoms, such as drug fever, arthritis, generalized lymphadenopathy	Simultaneous treatment with potentially interfering drugs
Drug-induced organ involvement, such as hepatitis, nephritis, pneumonitis or cytopenias, or severe eosinophilia	

AGEP - acute generalized exanthematous pustulosis; DHS - drug hypersensitivity syndrome; DIHS - drug-induced hypersensitivity syndrome; DRESS - drug reaction with eosinophilia and systemic symptoms; SJS - Stevens–Johnson syndrome; TEN - toxic epidermal necrolysis.

Both oral and parenteral routes can be used but oral routes appear to be safer. The starting dose ranges from 1/10,000 to 1/100 of the full therapeutic one, though it can be still be lower up to 1/1,000,000. Classical protocols for oral and intravenous desensitization to penicillin start at 1/10,000–1/100 of the target dose; doubled doses are administered every 15–20 minutes over the course of several hours until the therapeutic dose is reached. In general, a 12- to 16-step algorithm has been used successfully for a variety of drugs in patients with immediate hypersensitivity. A few sampled protocols are provided in the tables for penicillin desensitization procedure for oral, intravenous, as well as combined routes (Tables 48.3–48.5).

Table 48.3: Combined oral–subcutaneous–intramuscular penicillin desensitization protocol

Dose*	Units	Route
1	100	P.O.
2	200	P.O.
3	400	P.O.
4	800	P.O.
5	1600	P.O.
6	3200	P.O.
7	6400	P.O.
8	12,800	P.O.
9	25,000	P.O.
10	50,000	P.O.
11	100,000	P.O.
12	200,000	P.O.
13	400,000	P.O.
14	200,000	S.C.
15	400,000	S.C.
16	800,000	S.C.
17	1,000,000	I.M.

P.O. - oral; S.C. - subcutaneous; I.M. - intramuscular.
* The interval between doses is 15 minutes.

Table 48.4: Oral penicillin desensitization protocol

Step*	Penicillin (mg/mL)	Amount (mL)	Dose (mg)	Cumulative dose (mg)
1	0.5	0.1	0.05	0.05
2	0.5	0.2	0.1	0.15
3	0.5	0.4	0.2	0.35
4	0.5	0.8	0.4	0.75
5	0.5	1.6	0.8	1.55
6	0.5	3.2	1.6	3.15
7	0.5	6.4	3.2	6.35
8	5.0	1.2	6.0	12.35
9	5.0	2.4	12.0	24.35
10	5.0	5.0	25.0	49.35
11	50.0	1.0	50.0	100.0
12	50.0	2.0	100.0	200.0
13	50.0	4.0	200.0	400.0
14	50.0	8.0	400.0	800.0

*The interval between doses is 15 minutes.

Table 48.5: Intravenous penicillin desensitization protocol using continuous infusion pump

Step	Penicillin (mg/mL)	Flow rate (mL/hour)	Dose (mg)	Cumulative dose (mg)
1	0.01	6	0.015	0.015
2	0.01	12	0.03	0.045
3	0.01	24	0.06	0.105
4	0.1	5	0.125	0.23
5	0.1	10	0.25	0.48
6	0.1	20	0.5	1.0
7	0.1	40	1.0	2.0
8	0.1	80	2.0	4.0
9	0.1	160	4.0	8.0
10	10.0	3	7.5	15.0
11	10.0	6	15.0	30.0
12	10.0	12	30.0	60.0
13	10.0	25	62.5	123.0
14	10.0	50	125.0	250.0
15	10.0	100	250.0	500.0
16	10.0	200	500.0	1000.0

Desensitization in Delayed Drug Hypersensitivity[11]

There are, so far, no controlled studies available on desensitization in delayed-type HSRs to drugs. Single case reports to patient series of less than five patients to several dozens of patients per individual drug are reported with varying terminology, characterization of patients, practical aspects concerning desensitization e.g. dose increment, route of administration, time interval between incremental doses, number of days needed to reach a full therapeutic dose, and use of premedication. Among various CADRs, desensitization in delayed HSRs is used in mild, uncomplicated exanthems and fixed drug eruptions The most extensive literature exists on patients who have been desensitized with co-trimoxazole, particularly in HIV-positive patients. In delayed-type reactions, usually the oral route is chosen, depending on the drug formulation, and most often long protocols with repetitive, slow, gradually increasing doses have been used, which last from hours to days to several weeks. The occurrence of the first clinical symptoms of a recurred HSR may be delayed by 2–3 days. The procedure should mostly be done in a indoor hospital setup for practicability and optimal surveillance. Close monitoring of the patient by experienced physicians is strongly recommended with regular observations of the subjective and objective signs and symptoms. There is no universal

or consensus drug desensitization protocol to date for delayed-type HSRs. Protocols vary in the duration taken to achieve therapeutic dose, ranging from a few hours to several weeks. The starting dose may vary from one-millionth to one-eighth of the therapeutic dose. Many protocols are in fact "tailor-made" for each patient and each drug.

Two common clinical scenarios where one is often challenged with the issue of considering drug reintroduction in spite of severe reactions is, use of co-trimoxazole in HIV-positive patients, and treatment with multidrug antitubercular regimens.[19,20] Table 48.6 and 48.7 depict the protocol for desensitization with co-trimoxazole and antitubercular drugs, respectively.

PROBLEMS EXPECTED DURING DESENSITIZATION

Reactions may occur during desensitization and manifest as a wide range of symptoms characteristic of HSRs. *Cutaneous reactions* may include flushing, pruritus, urticaria, maculopapular erythemas, and angioedema. More severe reactions may encompass *cardiovascular manifestations*, such as chest pain, tachycardia, a sense of impending doom, presyncope, syncope, hypotension, and *respiratory symptoms* including sneezing, nasal congestion, dyspnea, coughing, wheezing. *Severe reactions* may also be characterized by throat tightness or gastrointestinal complaints, including nausea, vomiting, diarrhea, and abdominal pain.[21] For delayed type of hypersensitivity, reappearance of similar reaction can occur even after few days of therapeutic dose.[11]

Reactions during desensitization may need interruption of the infusion for a short while, followed by antihistamine administration. For severe reactions, systemic steroids can be given. Inj. epinephrine should be ready at bedside. On resolution of the reaction the protocol may be restarted from the step at which it had been discontinued. In certain rare scenario of severe reactions, one may need to consider to stop the process of desensitization.

Table 48.6: Protocol for oral desensitization of trimethoprim/sulfamethoxazole in HIV-positive patient

Dosing level	Portion of single strength of TMP/SMZ (%)	Amount (frequency) of TMP (40 mg)/ SMZ (200 mg) suspension (mL)	Total dose of TMP	Total dose of SMZ
1	12.5	1.25 (q.d.)	10	50
2	25	1.25 (b.i.d)	20	100
3	37.5	1.25 (t.i.d.)	30	150
4	50	2.5 (b.i.d.)	40	200
5	75	2.5 (t.i.d.)	60	300
6	100	One single strength tablet	80	400

TMP/SMZ - trimethoprim/sulfamethoxazole.

Table 48.7: Reintroduction schedule for antitubercular drugs in SJS[19]

Week	Day from start	Drug	Dose (mg)
1	1	EMB	200
1	3	EMB	400
1	5	EMB	600
1	7	EMB	800
2	9	INH	50
2	11	INH	100
2	13	INH	200
2	15	INH	300
3	17	RMP	150
3	19	RMP	300
3	21	RMP	450
3	23	RMP	600
4	25	PZA	250
4	27	PZA	500
4	29	PZA	1000
4	31	PZA	1500

EMB - ethambutol; INH - isoniazid; PZA - pyrazinamide; RMP - rifampicin.

LEARNING ESSENTIALS

- Desensitisation protocols are essential in situations where ADR to a drug exists but the use of the drug is a necessity.
- Recommended standardized protocols are available for immediate but not for delayed hypersensitivity reactions.
- Rapid desensitization protocols to treat immediate hypersensitivity reaction to agents such as penicillin, cephalosporin, other antibiotics, chemotherapeutic agents, and monoclonal antibodies are now available.
- In delayed type 4 reactions, gradual graded escalated doses of drugs are administered, under supervision. This may be done until drug tolerance develops. This has been attempted for tuberculosis therapy.
- Absolute and relative contraindications exist for attempting desensitisation. Severe reactions like SJS, TEN, DRESS and AGEP should not undergo desensitisation.
- A thorough counseling, consent, and discussion with the patient about the possible risks and benefits (benefit-risk assessment), indoor supervision and observation, are mandatory before undertaking such protocol.

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Chapter

49

Paradoxical Drug Reactions

Uwe Wollina

SUMMARY

Paradoxical drug reactions are nonallergic drug reactions with an outcome of treatment opposite of the expected one. They are often perplexing to clinicians. This chapter provides a brief historical reminiscence along with an overview about the possible mechanisms. Paradoxical reactions to antimicrobial, antiviral drugs, antimalarial drugs, antihistamines, classical systemic immune suppressants, biologics, antineoplastic drugs, and neuromodulators are described in this chapter along with treatment options. Early recognition of paradoxical drug reactions is important for clinicians.

INTRODUCTION

Paradoxical drug reactions (PDRs) are known since the turn of the nineteenth to the twentieth century. The first well-described PDR was Jarisch–Herxheimer reaction (JHR) in treated syphilis patients. In 1895, Jarisch reported on temporary aggravation of mucocutaneous syphilitic lesions after initiation of mercury therapy.[1] In 1902, Herxheimer reported four syphilitic men treated with mercury who developed fever, anorexia, and sweating within 24 hours after the first dose [2] This was the classical triad accompanied by temporary aggravation of preexisting mucocutaneous lesions.

DEFINITION OF PARADOXICAL DRUG REACTIONS

PDRs are drug reactions with an outcome opposite of the expected one. Three different types of PDR have been defined as follows:

1. A condition or disease for which the drug is being registered and/ or explicitly prescribed.
2. A precipitation of a condition or disease for which the drug is registered and/or indicated, while the drug is being used for another indication.
3. Drug reactions that seem to be paradoxical according to known facts of their pharmacologic effects but unrelated to the approved indication.

PDRs have to be separated from unanticipated drug reactions.[3] Different mechanisms have been considered as being responsible for PDR (Table 49.1).

Table 49.1: Mechanisms of paradoxical drug effects

Mechanism	Remarks
Hormesis	Characterized by opposite drug effects at different drug concentrations.
Complex systems	Complex systems are dynamic; they occur at different levels (i.e. tissues, cells, receptors) resulting in a diversity of etiologies that cannot be explained by a single general mechanism.
	Some examples include (a) single target, partial agonist; (b) single target, stereochemical effects; (c) single target, time-dependent downstream effects; and (d) single target, interference with oscillatory systems.
	Examples for multiple targets or systemic levels include (a) time-dependent effects, (b) antibody-mediated reactions, (c) response overcompensation, or (d) altered function at higher level.

Source: Smith et al.[3]

This chapter discusses different types of PDRs to various classes of drugs.

ANTIBIOTICS AND ANTIVIRAL DRUGS

The reproduction or aggravation of infectious disease symptoms is known as JHR. The clinical symptoms include chills, fever, headache, myalgia, and exacerbation of mucocutaneous lesions. JHR has been described for syphilis, borreliosis, leptospirosis, mycobacterial diseases, and Q fever among others.[4] JHR is dependent not only on the immune status of patients but on treatment as well. In HIV-positive patients presenting with early syphilis, the risk of JHR was found to be higher with benzathine penicillin G compared to 2 g azithromycin given once orally.[5]

Another possible PDR is the immune reconstitution inflammatory syndrome (IRIS) that has been noted in patients with HIV/AIDS during highly active antiretroviral therapy (HAART). In a randomized trial with 597 Cambodian patients who were naïve for antiretroviral therapy (ART), with CD4 cell counts ≤200 cells/μL, and who were newly diagnosed tuberculosis (TB) after ART initiation, the rate of paradoxical TB-associated IRIS was 26%. Symptoms included fever, progressive lymphadenopathy, and worsening or appearance of new radiologic findings. TB-IRIS was seen to occur more frequently in patients with early initiation of ART but easily manageable.[6] Higher rates of paradoxical TB-IRIS have also been reported from South Africa when ART was started within 4 weeks after TB treatment (19.5%) compared to late integrated (7.5%) or sequential treatment (8.1%). This study also reported more severe TB-IRIS, higher hospitalization rates, and longer time for resolution.[7]

Severe paradoxical skin reactions have also been noted in HIV/AIDS patients with Buruli ulcers caused by *Mycobacterium ulcerans* and treated by antibiotics after ART initiation. In one study from Australia, the rate of IRIS was 21%, developing, after a median of 39 days from initiation of antibiotic treatment. Inflammation, tissue necrosis, and enlargement of wound were associated with edema and pain. New ulcers may develop distant from the original ones. The paradoxical reaction responds to systemic corticosteroids.[8,9]

In countries like India where leprosy is common in occurrence, precipitation of type I lepra reaction in borderline leprosy after the start of multi-drug therapy (MDT) is very common in which new lesions of leprosy appear in addition to reactional change in the existing patches. This usually occurs due to upward shift in cell mediated immunity (CMI) due to killing of bacilli by anti-leprosy drugs.

ANTIMALARIAL DRUGS

Chloroquine and hydroxychloroquine are antimalarial drugs used to treat polymorphic light eruption.[10] In rare cases, however, these drugs can cause photodermatosis resembling polymorphic light eruption.[11]

ANTIHISTAMINES

Hydroxyzine is a sedating first-generation H1 receptor inhibitor occasionally used for pruritic dermatoses including urticaria. Cetirizine is a selective second-generation H1 receptor inhibitor without central nervous system suppression. It is used in allergic rhinitis, atopic dermatitis, and treatment of urticaria. However, there have been reports on paradoxical acute exacerbation of preexistent chronic idiopathic urticaria either by intolerance reaction or by type I hypersensitivity reaction.[12,13]

CLASSICAL IMMUNOSUPPRESSIVE DRUGS

Severe cutaneous adverse reactions are Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), and drug reaction with eosinophilia and systemic symptoms (DRESS). A systematic review from India reported a mortality rate of 16.4% in SJS/TEN.[14] Key mediators of SJS/TEN are as follows:

1. Granulysin: A cytolytic multifunctional saposin-like protein presented in cytotoxic T-lymphocytes and natural killer cells involved in epidermal keratinocyte death.
2. Perforin and granzyme, which attenuate keratinocyte cytotoxicity.
3. Fas (death receptor)/Fas ligand interaction leading to cell lysis.
4. Cytokines and chemokines such as tumor necrosis factor-alpha (TNF-α), interferon-γ, caspase, CCR, and CXCR chemokines.

The mainstay of treatment are systemic corticosteroids, but other classical immunosuppressive drugs such as azathioprine or cyclosporine A have also been used.[15,16] In Japanese patients, many cases of azathioprine-induced SJS/TEN have been seen.[17,18]

Methotrexate is an antifolate drug used systemically in low doses to treat psoriasis or autoimmune connective tissue disease. Methotrexate-induced papular eruption is a PDR that develops early after initiation of treatment. It is a pruritic disorder with disseminated papules preferably located on the proximal extremities. Histiocyte rosettes around thick dermal collagen bundles intermingled with a few neutrophils are seen in skin biopsies.[19,20]

BIOLOGICALS

Biologicals or biopharmaceuticals are drugs produced in or extracted from living organisms or semi-synthesized from biological sources. TNF-α inhibitors have the broadest indications in medicine. In dermatology, they are approved for psoriasis, psoriatic arthritis, and hidradenitis suppurativa. In hidradenitis suppurativa only adalimumab is approved. They can be subdivided into antibodies directed against receptors (infliximab, adalimumab, golimumab) or receptor antagonists (etanercept).

TNF-α inhibition has been investigated in a number of prospective randomized controlled trials in psoriasis and has become an established therapy for moderate-to-severe plaque-type psoriasis. However, plaque psoriasis, nail psoriasis, intertriginous, erythrodermic, and palmoplantar pustular psoriasis may be induced or aggravated with a mean time of 9.5 months after initiation of TNF-α inhibition (Figs. 49.1 and 49.2). In a study covering 120 patients with this PDR (mean age 42.3 years), newly induced psoriasis was observed in 62% and aggravation or exacerbation of a preexisting psoriasis was observed in 38%. Women predominated twice as much as men due to the larger group of rheumatic diseases.[21] Another analysis of patients with chronic inflammatory bowel disease (CIBD) treated by TNF-α inhibitors identified 222 patients with psoriasis as a PDR. Their mean age was 26.5 years with a balanced sex ratio. About 78% of these patients had Crohn's disease. Only 8% developed palmoplantar pustular psoriasis.[22] The cumulative incidence of TNF-α inhibitor-induced psoriasis among patients with CIBD has been estimated as high as 3.5%–10.1%.[23,24] This rate is much higher than that among patients with rheumatoid arthritis. The British Society for Rheumatology Biologics Register reported an incidence of 1%.[25] Younger age and higher doses of anti-TNF-α were identified as possible risk factors in CIBD.[23]

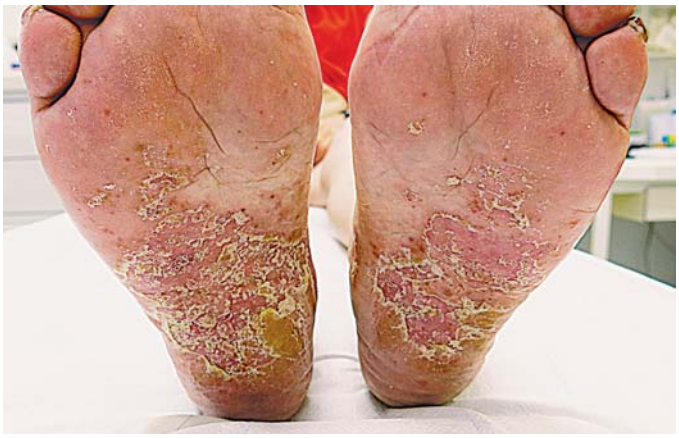

Fig. 49.1: Palmoplantar psoriasis in a patient of Crohn's disease treated with adalimumab.

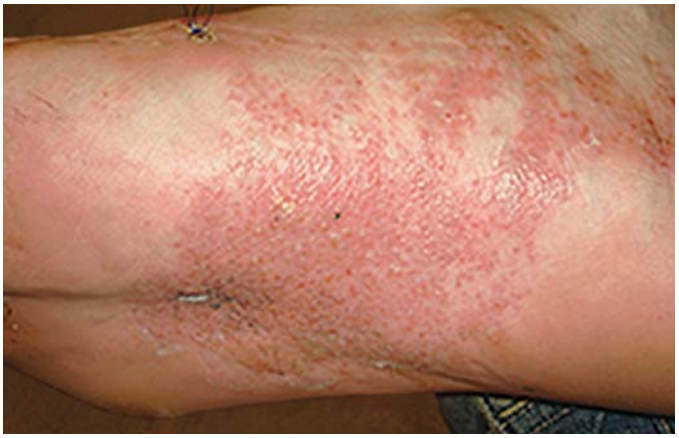

Fig. 49.2: Palmoplantar pustulosis in a patient of rheumatoid arthritis treated with infliximab.

In addition, the induction of psoriatic arthritis has been reported in patients, mostly with Crohn's disease.[26,27]

The mechanism behind this PDR is not clear. Since plasmacytoid cells are involved in psoriasis pathogenesis and are down regulated by TNF-α, TNF-α inhibition may activate these cells that are potent interferon-α producers.[28] Interferon-α can induce or aggravate psoriasis.[29] Additional pathways may involve over expression of regulated on activation normal T cell expressed and secreted (RANTES), chemokine ligands (CXCL), and metalloproteinase 2 and 9.[30]

Treatment is dependent on the body surface affected and the severity of inflammation. Most patients can be treated topically by corticosteroids and vitamin D analogs. Cessation of treatment is not mandatory.[21]

Another paradoxical reaction of TNF-α inhibitors is the induction of acne inversa/hidradenitis suppurativa after a mean duration of 12 months of treatment. Adalimumab was the most frequent biological associated with this paradoxical reaction although it is also the only one with an approved indication for acne inversa/hidradenitis suppurativa. Complete improvement was observed in most cases after either cessation of biologics or switch over to another biological.[31]

Tocilizumab, a humanized antibody against interleukin-6 receptor, is used to treat various rheumatic diseases such as rheumatoid arthritis, juvenile idiopathic arthritis, or adult-onset Still's syndrome. The drug can cause paradoxical reactions such as psoriasis.[32]

A rare form of drug-induced lupus-like syndrome of unknown etiology caused by TNF-α inhibitors, known

as TNF-α antagonist-induced lupus-like syndrome (TAILS), often occurs in women in their fifth decade of life. Its overall incidence has been estimated to be 1% among patients with CIBD. The various hypotheses debated in the pathogenesis of TAILS are as follows:

1. Release of lupus autoantigens due to apoptosis induction in inflammatory cells by TNF-α inhibitors.
2. Increased infection rate with subsequent activation of B lymphocytes and the production of autoantibodies during TNF-α inhibitor therapy.

TAILS can present either as a limited cutaneous reaction with antinuclear and anti-ds DNA autoantibodies or like systemic lupus erythematosus with additional extracutaneous symptoms and multiorgan affection (Fig. 49.3). The reported odds ratios for this PDR are higher with monoclonal antibodies than with receptor antagonist.[34] TNF-α inhibitor treatment has to be stopped only in those patients with the latter type.

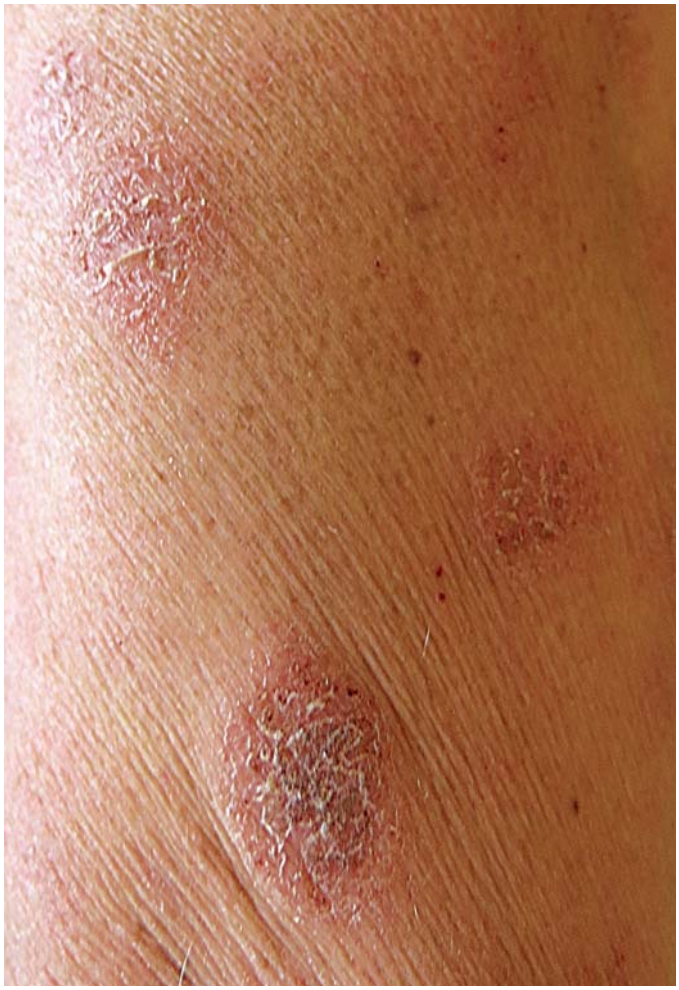

Fig. 49.3: TNF-α antagonist-induced lupus-like syndrome (TAILS) in a patient of Crohn's disease treated with infliximab. Lesions resemble subacute cutaneous lupus erythematosus.

TNF-α inhibitors have been used occasionally in SJS/TEN.[35] However, these drugs may also induce SJS/TEN in rare cases. Patients with the highest risk for this PDR are women with rheumatoid arthritis.[36] Omalizumab is the first anti-IgE monoclonal antibody approved for the treatment of moderate-to-severe chronic idiopathic urticaria. Occasionally, a paradoxical induction of urticaria or even anaphylaxis may occur.[37]

ANTINEOPLASTIC AGENTS

Inhibitors of epidermal growth factor receptor (EGFR) are targeted chemotherapeutic agents approved for different cancers, including squamous cell carcinoma (SCC) of the head and neck. There are two classes of these inhibitors: (a) monoclonal antibodies such as cetuximab, panitumumab, and matuzumab binding to the extracellular tyrosine kinase domain of EGFR, and (b) small-molecules-blocking tyrosine kinase such as erlotinib, gefitinib, lapatinib, or afatinib.

Trichomegaly and hypertrichosis are known adverse effects as hair follicles express EGFR. PDRs include non-scarring alopecia in the form of patchy or frontal alopecia, which occurs usually with a delay of 2–3 months after initiation of treatment.[38]

Oncogenic activation of BRAF stimulates cancer growth by promotion of Ras-independent mitogen-activated protein kinase (MAPK) pathway signaling. BRAF inhibitors (vemurafenib, dabrafenib) are used for the treatment of advanced melanoma. Related to a paradoxical activation of MAPK signal transduction, patients can develop acantholytic dyskeratosis resembling Grover's disease (Figs. 49.4 and 49.5). For the treatment of these lesions emollients have been recommended.[39,40]

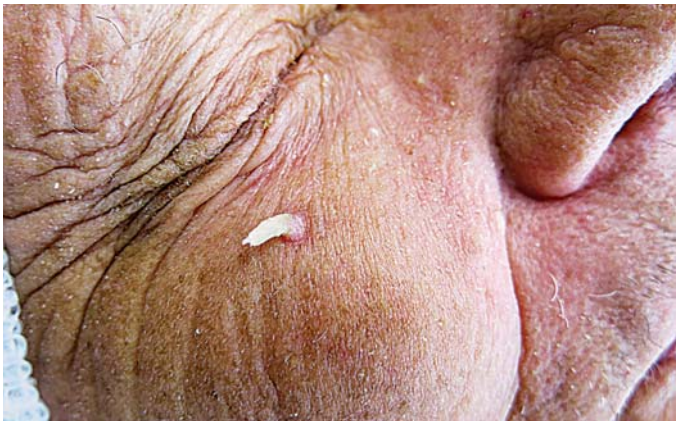

Fig. 49.4: Spiky keratotic lesions induced by BRAF inhibitor vemurafenib in a patient with advanced melanoma.

But it is not only the development of benign lesions. Since BRAF inhibitors may either inhibit or paradoxically stimulate the MAPK pathway, this

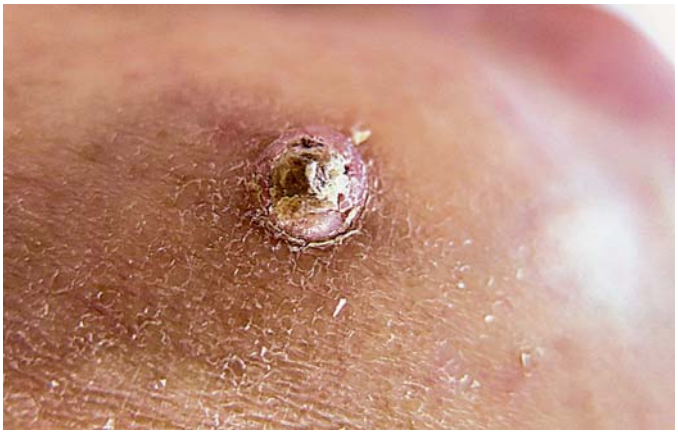

Fig. 49.5: Dyskeratotic acantholytic papule during BRAF-inhibitor (vemurafenib) therapy of advanced melanoma.

can cause nonmelanoma cancer growth. In cells that express the same HRAS mutation observed in SCC, BRAF inhibitor vemurafenib stimulated growth and induced the expression of MAPK pathway response genes.[41] Indeed, SCCs are the most common tumors in patients treated with BRAF inhibitors (Fig. 49.6).[42] By combining BRAF inhibitor with an MEK-inhibitor for advanced melanoma the rate of SCC development can be reduced.[43]

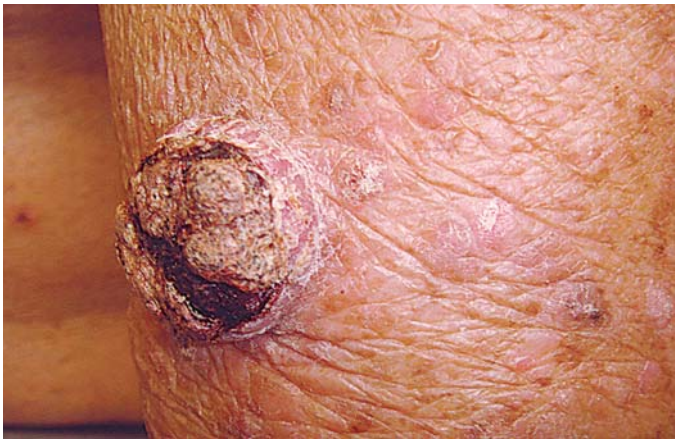

Fig. 49.6: Multiple keratotic lesions, one larger keratoacanthoma-like squamous cell carcinoma (SCC) in a patient with advanced melanoma treated by vemurafenib (BRAF inhibitor).

Vismodegib is a hedgehog inhibitor approved for drug therapy of advanced, nonresectable or metastatic basal cell carcinoma. Failure to treatment may result from primary or secondary tumor resistance.[44] However, it has been reported recently that during vismodegib therapy aggressive SCC may develop.[45,46] The authors hypothesized that squamous cells of metatypic basal cell carcinomas may benefit from hedgehog inhibition.

A larger study from California analyzing 180 patients treated with vismodegib demonstrated predisposition to develop other cutaneous tumors with a hazard ratio of 6.37. The hazard ratio for SCC was 8.12. These patients require a lifelong dermatologic surveillance.[47] The cause of this predisposition remains to be elucidated.

Sorafenib is a small-molecule inhibitor of the tyrosine kinase domain of vascular endothelial growth factor used in targeted therapy for hepatocellular carcinoma and lung cancer. There are reports of paradoxical induction of psoriasis during sorafenib therapy.[48] BRAF inhibitor dabrafenib has also been reported to induce psoriasis.[49]

Immune checkpoint inhibitors have become available for advanced melanoma and other cancers. The following monoclonal antibodies against programmed cell death-1 (PD1) have been investigated: Nivolumab, pembrolizumab, pidilizumab, and atezolizumab. A recent review listed 21 patients of whom 71.4% had mild psoriasis and developed psoriasis flares during anti-PD1 therapy. The flares occurred earlier in patients with psoriasis compared to psoriasis-naïve patients.[50]

NEUROMODULATORS

Capsaicin (8-methyl-N-vanillyl-6-nonenamide) is the active ingredient of chilies, belonging to transient receptor potential family of ion channels called vanilloid (TRPV), provoking burning sensations and wheal-and-flare responses. A single application of capsaicin causes pain whereas repeated application induces analgesia due to desensitization of C-fibers.[51] For instance, capsaicin 8% topical patch (Qutenza®) is used for postherpetic neuralgia relief.[52]

Botulinum toxin A (BoNT/A) is produced by *Clostridium* spp. Seven different serotypes have been identified. BoNT/A is a Zn^{2+}-endopeptidase that cleaves SNAP-25, which is involved in the assembly of the SNARE (soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor) complex. This results in a blockade of acetylcholine release from the presynaptic neuronal membrane.[53] Other neurotransmitters blocked by BoNT/A are substance P and calcitonin gene–related product, which are involved in chronic headache.[54] BoNT/A is used in aesthetic medicine to reduce rhytides, particularly in the upper third of the face. Patients reported from time to time that their tension headaches or migraine has become better.[55] Such observations stimulated investigations in primary headaches such as migraine and tension-type headaches.[54,56] However, about 1% of patients treated with BoNT/A injections of the forehead and glabella region may experience severe and debilitating headaches, which persist 2–4 weeks before fading gradually.[57] The mechanism for this PDR is unknown.

LEARNING ESSENTIALS

- PDRs are part of drug-related unwanted side effects. Paradoxical drug reactions are nonallergic drug reactions with an outcome of treatment opposite of the expected outcome. They are not rare.
- Paradoxical IRIS and induction of psoriasis by biologicals have been observed in increasing numbers.
- The mechanisms behind PDR are not completely understood but do not seem to be uniform at all.
- Knowledge of PDRs is important to recognize these reactions early and to treat them properly.

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Chapter

50

Reporting of Adverse Drug Reaction: Pharmacovigilance

Sushil Pande

SUMMARY

Pharmacovigilance is a mechanism of reporting and analysis of adverse reports of drugs, the outcome of which is conveyed to clinicians for improving drug safety. In clinical practice, safety of a drug and it's efficacy are equally important. Side effects of medications are frequently encountered in day-to-day practice; however, they are not actively reported or shared among clinicians. Pharmacovigilance involves reporting of such adverse drug reactions (ADRs) by clinicians and pharmacists. Data thus generated is analyzed by a group of experts to generate a "safety signal". This safety signal is then dealt with by regulatory authorities who pass on the information to drug manufacturers to generate additional safety data. Final updated safety information is then passed onto clinicians who prescribe the drug based on a risk-benefit analysis(risk management). The reporting of ADRs helps in continuous updation of safety information with respect to individual drugs in an attempt to enhance drug prescription safety.

The methods and implications of ADR reporting are discussed in the following sections.

WHY IT IS REQUIRED IN DERMATOLOGY?

Adverse event (AE) or adverse drug reactions (ADRs) should be reported by all practicing clinicians. This also applies to dermatology physicians. Dermatologists are at a distinct advantage of recognizing the adverse reactions from drugs due to easy visibility of rash in the skin and contribute significantly to generate safety data on drugs. Current situation in dermatology practice warrants use of proactive and more efficient reporting of AEs/ADRs. With the sudden influx of various dermatology and cosmeceutical preparations into the Indian market, dermatologists are puzzled about the rationale of such formulations. Scientific information and critical analysis of various drug formulations or drug combinations are generally lacking. Therefore, a need to highlight adverse reactions and adverse cutaneous drug reactions encountered in clinical practice is strongly felt.

Many drugs that enter the market come through clinical trials, where the drug is tested in a controlled environment, in a small number of patients and safety data are generated for a short term, for the period of clinical trial alone. Most of us refer to these data while prescribing a drug to the patient. Pharmacovigilance provides active surveillance of drug safety behavior in actual "real-life", clinical practice. This also applies to dermatology where newer biologics, antihistamines, immunosuppressive agents, and many other new systemic drugs enter into the market through clinical trials, with availability of only short term safety data.

WHO CAN REPORT ADR?

In India, it is a myth that pharmacovigilance is the domain of pharmacologists. In fact, the basis of pharmacovigilance is ADR reports submitted by clinician. Hence, private practitioners and consultants should actively report drug reactions. *Stakeholders in adverse event (AE) reporting are clinicians, pharmaceutical industries, regulatory authorities, and patients.* Pharmaceutical industries are mandated to submit data about drug safety; both as obtained through controlled clinical trials as well as through data generated in

post marketing surveillance. (real-life situation or actual practice). Besides this, clinicians, pharmacists, or patient/patient groups can directly report information about drug side effects to regulatory authorities. This includes food and drug administration (FDA) in United States, European Medicines Agency (EMA) in European Union, Medicines and Health Regulatory Agency in the United Kingdom, and Central Drugs Standard Control Organization (CDSCO) in India.[1] Drug Controller General of India (DCGI) is a part of CDSCO. As patients are end consumers of the drug, they have well within their rights to report AEs. This is usually done by alert or educated patients. However, in India, reporting by patients is very seldom resorted to. Hence, the role of reporting by health-care provider or doctors is extremely important. Doctors should ensure that a particular drug is prescribed to a patient only after risk–benefit analysis is taken into consideration and all labeling information about drug safety is assessed in a scientific manner.

HOW ADVERSE REACTION IS REPORTED?

AE or ADR is reported through a simple proforma (Appendix-5). *Essential components of reporting are identifiable patient, reporting doctor/person, suspected drug/drugs, and nature of AE/ADR.* Any unusual rash and serious reactions should always be reported. It is desirable to report the exact morphology of cutaneous drug reactions, as fixed drug eruption (FDE), maculopapular rash, urticarial rash, lichenoid rash, or toxic epidermal necrolysis (TEN). This helps manufacturers or regulatory authorities to mention specific type of drug reaction in package insert or label. ADR reporting form (Appendix 5) used in Pharmacovigilance Programme of India (PvPI)[2] is available at http://www.ipc.gov.in/PvPI/ADRReportingForm.pdf. Such forms can also be collected from pharmacology departments of all medical colleges in India, which are recognized as peripheral pharmacovigilance centers under Indian government's PvPI.

WHAT IF DERMATOLOGIST/CLINICIAN IS NOT SURE ABOUT ADR?

In dermatology or clinical practice, it is often difficult to ascribe the rash in question to be induced by a particular drug, as the patient may be on multiple drugs. Confounders like viral infections, food, etc. may also be an inducer of the rash. In such a situation, clinician should make a detailed report of suspected AE/ADR based on clinical suspicion alone. Causality assessment is usually done by experts after the report is submitted to regulatory authorities.

WHAT HAPPENS TO SUBMITTED REPORTS? (PROCESSES/STEPS IN PHARMACOVIGILANCE)

When AE/ADR report is submitted to regulatory authorities, a formal process is followed in pharmacovigilance (Fig. 50.1).[1] The pyramid in the figure highlights the steps involved, namely-

1. Collection of safety data;
2. Processing and databasing of safety data;
3. Safety signal detection;
4. Retrieval and analysis of safety signal related data;
5. Communication of results of analysis to stakeholders;
6. Active risk management.

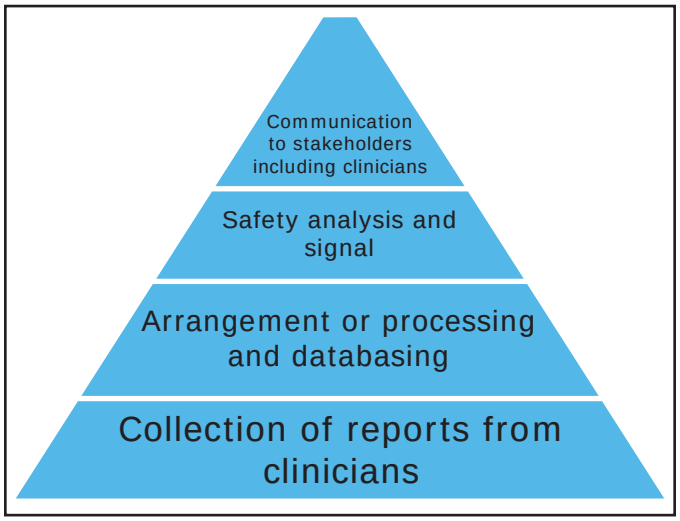

Fig. 50.1: Pyramid illustrating steps in pharmacovigilance.

Step 1: Collection of Report from a Clinician

This is the basic and the most important step in pharmacovigilance. Information written in this report is crucial and forms the basis of conclusions arrived at, in the processes that follow subsequently. This emphasizes the role of clinicians and the need for proper and complete reporting of AE/ADR.

Step 2: Arrangement or Processing and Databasing of Safety Data

When multiple reports are submitted, only reports that are complete and contain the four essential components of the event or reaction (identifiable patient, reporting doctor/person, suspected drug/drugs, and nature of AE/ADR) are considered for further processing. Hence, reports should be complete. All data are arranged with the help of MedDRA dictionary, which is commercially available. A specific term is designated to symptoms, signs or diagnosis as reported by clinicians.

Step 3: Safety Signal Generation and Analysis of Safety Signal-Related Data

On the basis of reports, as per the format prescribed, cumulative data are analyzed, usually by experts and pharmacologists.

If there is conclusive and statistically significant evidence of safety, with respect to a particular drug, a *drug safety alert or signal* is generated. Global pharmacovigilance center analyzes these data. If needed, it can ask regulatory authorities to submit more data through clinical studies.

Step 4: Communication of Results to Stakeholders and Active Risk Management

On the basis of the drug safety report and scientific evidence for a particular ADR, results of analyzed data are conveyed to stakeholders. If there are serious or life-threatening ADR to a particular drug, the drug can be banned through appropriate mechanism(s). Changes in the labeling information are also done accordingly.

World Health Organization (WHO)–Uppsala Monitoring Centre (WHO-UMC) is the apex global pharmacovigilance center located at Uppsala, Sweden. WHO-UMC coordinates all these activities where international adverse reaction data are analyzed and safety alerts are generated. It not only provides tools for data entry, retrieval, reference, and research but is also involved in education, training, and functional aspects of national pharmacovigilance centers across the world.[3]

WHAT IS PVPI PROGRAMME?[4]

In India, CDSCO initiated a nationwide pharmacovigilance program in July 2010, with the All India Institute of Medical Sciences (AIIMS), New Delhi, as the National Coordinating Centre (NCC) for monitoring ADRs in India so as to safeguard public health. The NCC was then shifted to the Indian Pharmacopoeia Commission, Ghaziabad, (Uttar Pradesh) in April 2011.

The mission of PvPI is to safeguard the health of the Indian population by ensuring that the benefit of the use of medicine outweighs the risks associated with its use.

- The purpose of the PvPI is to collect data, analyze it, and use these inferences to recommend informed regulatory interventions, besides communicating risks to health-care professionals and the public.
- The vision of PvPI is to improve patient safety and welfare in the Indian population by monitoring drug safety and thereby reducing the risk associated with the use of medicines.

The program has been implemented in various phases; initiation phase (2010–2011), expansion and consolidation phase (2011–2012), expansion and maintenance phase (2012–2013), expansion and optimization phase (2013–2014), and excellence phase (2014–2015).

The program functions through ADR monitoring centers (AMCs), which collaborate with Central Drug Standard Control Organization (CDSCO) zonal centers (North, South, East, and West). As on the end of 2014, there were 90 AMCs including 70 governmental and 20 nongovernmental institutions, which reported more than 74,000 individual case safety reports. An additional number of 140 institutions have been proposed as AMCs, which include 51 governmental and 89 nongovernmental institutions. Medical colleges function as AMCs.

CHALLENGES IN ADR REPORTING

Despite its proven effectiveness, ADR reporting in India is far from satisfactory. This also applies to dermatology practice. There are multiple reasons with regard to all stakeholders involved in drug practice.

1. Increased patient load and lack of time for dermatologists.
2. Lack of knowledge and information about methods of reporting.
3. Lack of motivation to report.
4. Lack of communication and collaboration between dermatologists and CDSCO.
5. Poor education status of patients and decreased awareness of side effects.
6. Lack of proactive approach by pharmaceutical companies to generate clinical safety data.
7. Lack of effective laws for manufacturers.

FUTURE OUTLOOK

With increased awareness among doctors and patients about side effects of drugs used in modern medicine and increasing implementation of effective pharmacovigilance program by Government of India, drug safety reporting and other safety related activities are bound to increase in the near future. As dermatologists, we have a greater role to play in pharmacovigilance, by reporting cutaneous and systemic side effects of drugs used in our practice.

LEARNING ESSENTIALS

- Reporting of ADRs or adverse drug cutaneous reactions should be actively done by dermatologists to update safety information of drugs being used.
- In India through PvPI, reporting of ADR is done in the format given by CDSCO, which is simple and less time-consuming.
- Reporting of ADR should be done even in suspected cases of ADR and not just when ADR is confirmed or causal association to drugs is ascertained.
- Identifiable patient, reporting doctor/person, suspected drug/drugs, and nature of AE/ADR are the only four essential components when ADR is reported.
- When there are multiple case reports of valid reported ADR, regulatory authorities have power to influence manufacturing and marketing approval of unsafe drug or practice of unsafe drugs. This is very relevant in a country like India where large number of dermatology drugs (like topical corticosteroids) are often misused and even prescribed by nonexperts or unqualified physicians.

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Chapter

51

Legal Issues and Counseling in Cutaneous Adverse Drug Reaction

Subodh Sirur

SUMMARY

Though incidence of severe forms of cutaneous adverse drug reactions is relatively uncommon, when they do occur, it can result in significant morbidity or mortality which in turn can result in litigation. Simply because a drug reaction has occurred does not implicate a doctor for medical negligence. However, failure to diagnose the drug reaction and manage the drug reaction appropriately in time can lead to a liability for medical negligence. Counseling of the patient and relatives forms an important step in dealing with a case of drug reaction.

INTRODUCTION

A professor in a medical college during his ward rounds asked a resident the side effects of a particular drug. When most of the side effects had been mentioned by the resident and the professor was looking for further responses, the resident quipped "litigation".[1] Indeed, litigation can occasionally result from a cutaneous adverse drug reaction. A majority of cutaneous adverse drug reactions are likely to be mild and self-limiting and would not result in the patient taking a legal recourse.

A cutaneous adverse drug reaction can in rare cases result in either morbidity or mortality. While toxic epidermal necrolysis (TEN) remains a cause for mortality in the best of centers, Stevens–Johnson syndrome (SJS) is known to be associated with eye-related complications. Under such circumstances, the patient or the patient's legal representatives are more likely to pursue legal action against the doctor.

CUTANEOUS ADVERSE DRUG REACTION AND PROFESSIONAL NEGLIGENCE?[1]

Does the mere occurrence of a cutaneous adverse drug reaction implicate the doctor for professional negligence?[1] The answer to this question has certainly to be in the negative. There are certain drugs that are relatively safer and others that involve a greater amount of risk of adverse reactions, but the fact is that intake of any medication is known to be associated with adverse reactions. Further, it is not always possible to predict the adverse reaction in a given patient. Therefore, the occurrence of a cutaneous adverse drug reaction, by itself, will not indicate negligence on the part of the treating doctor.

In a particular legal case of alleged medical negligence, an appeal was filed before the State Commission, West Bengal, against the decision of the District Forum directing payment of compensation of Rs. 5,50,000 to a complainant for professional carelessness and negligence in the management of the drug reaction of the complainant's daughter. The facts of the case were as follows: The deceased daughter was suffering from bipolar affective disorder and was prescribed tablet Depakote (divalproex sodium). Later, she was also prescribed Lamitor© OD along with other medicines. Subsequently, she developed TEN and died due to septicaemia and non-cardiogenic pulmonary edema. A complaint was filed before the District Forum alleging negligence in prescribing the aforesaid drugs and that too in high doses, which was responsible for the death. The District Forum awarded compensation to the complainant against which an appeal was filed before the State Commission. Here during hearings, independent experts opined that the drug is approved for use in bipolar affective disorder and the dose prescribed was within the therapeutic limit. Further, that every medicine is known to have some reaction or other and that such a drug reaction is uncommon and rare. There was no evidence that the doctors

on hospitalization had erred in the management of TEN. Based on the expert opinion of a psychiatrist and a dermatologist, the State Commission held that there was no evidence to substantiate the allegations levelled against the doctors and the nursing home. The State Commission allowed the appeal and set aside the decision of the District Forum granting compensation to the complainant.[2]

WHO HAS ONUS OF PROVING NEGLIGENCE?

The onus of proving negligence is ordinarily on the person alleging negligence. The complainant is bound to prove the negligence and the allegations. It is only under certain circumstances such as "*res ipsa loquitur*" (the thing speaks for itself), the doctor is required to disprove the allegations. For example, in case of gauze piece left in the abdomen after a surgical procedure. The very fact that the gauze piece is left behind indicates negligence and the thing speaks for itself and no further proof of negligence is required.

WHY QUALIFICATION OF A TREATING DOCTOR IS SO IMPORTANT?

A doctor is duty bound to take care in treating his patient. The doctor has a duty of care in deciding whether to treat a patient who has presented to him/her for treatment; a duty of care in deciding what treatment to give, and a duty of care in the manner of administration of the treatment. When a drug reaction occurs, the Courts will examine if the drug suspected to have caused the drug reaction has been prescribed or administered by a doctor who has the requisite qualification to treat that particular ailment. Further, if the drug was indicated for that ailment and whether the manner of administration of the drug had been correct.

IMPORTANCE OF TIMELY REFERRAL

In a particular case, a patient was diagnosed by a nondermatologist to be having Hansen's disease on the basis of hypopigmented lesions on the forearms and was started on multidrug therapy. The patient developed an adverse cutaneous drug reaction to tablet dapsone. The physician had erroneously diagnosed the ailment to be Hansen's disease when in fact the patient had polymorphous light eruption. Fortunate for the patient, a dermatologist was called in and dapsone was discontinued and appropriate therapy was instituted.[1] This also highlights the fact that in most instances it is the dermatologist who plays a pivotal role in making a diagnosis of the cutaneous adverse reaction to a drug that is prescribed by another doctor.

In a case decided by the National Consumer Disputes Redressal Commission (referred to as National Commission in short), a boy of about 8 years with fever, cough, and cold presented to a general physician who prescribed him a sulfonamide along with antihistamine and antipyretic. The child developed swelling of the lips and blisters in the mouth and over different parts of the skin. A diagnosis of measles was made. Later, a referral was made to a pediatrician who concurred with the opinion of the general physician that the child was suffering from measles. As there was no improvement in the condition of the child, he was advised to be hospitalized. Nearly 36 hours following the hospitalization and further deterioration, a referral was made to an ENT surgeon who made the diagnosis of SJS. A dermatologist was then called in for the management of SJS. There was permanent damage to the eyes leading to severe impairment of vision and inability to even keep eyes open.

A complaint was filed before the State Consumer Disputes Redressal Commission claiming a compensation of Rs. 9.95 lakhs. The State Commission held the pediatrician liable for medical negligence and awarded compensation in favor of the complainant. An appeal was filed before the National Commission. The National Commission after perusal of the medical records and the medical literature arrived to a conclusion of negligence on the part of the general physician, the ophthalmologist, and the hospital and awarded a compensation of Rs. 5 lakhs along with interest. In this case, the dermatologist and the ENT surgeon were not made party to the complaint. In fact, they had made the diagnosis in time and appropriate therapy had been commenced.[3]

The above case law highlights the importance of making a referral to a specialist in time. Failure to diagnose a cutaneous adverse drug reaction may not be a negligent act but failure to refer to a specialist in time may result in negligence from legal perspective. TEN and SJS require a multidisciplinary management strategy and therefore referral to ophthalmologist and dermatologist would be essential. Management in an intensive care setting would be also required. Therefore, a prompt referral to the specialist and institution of appropriate therapy is imperative in cases of severe forms of drug reactions. Mere occurrence of a cutaneous drug reaction may not amount to negligence but failure to diagnose in time or failure to refer to a specialist in time or to manage the patient appropriately can amount to negligence.

FAILURE OF DUTY OF CARE AMOUNTS TO NEGLIGENCE

A wife of a doctor settled in the United States came to India on a holiday. She developed some skin rashes

for which she presented to a doctor who diagnosed her ailment as "vasculitis." As the condition of the patient continued to worsen, she was hospitalized to a tertiary care center. She was diagnosed to be having TEN. However, the cause of TEN could not be ascertained. When the condition further deteriorated, the patient was flown to Mumbai. The patient later died of septicemia. The husband filed a complaint before the National Consumer Disputes Redressal Commission claiming compensation for the negligence on the part of the doctors in the medical management. The National Commission dismissed the complaint. The husband challenged its decision before the Supreme Court.

The Supreme Court observed that the deceased patient was prescribed tablet prednisolone in the dose of 120 mg/day for 7 days and injection Depo-Medrol© intramuscular twice a day for 3 days prior to commencement of prednisolone. Depo-Medrol© is a depot preparation and is not administered twice daily as opined by the experts. The Supreme Court held the doctor negligent for prescribing a long-acting steroid and an excessive dose of corticosteroid without foreseeing its implication. The medical literature was filed before the Supreme Court, which noted two schools of thoughts pertaining to the use of corticosteroids in TEN. It also noted that the pro-steroid group recommended the use of corticosteroids in the initial stage of the disease only as there is a higher risk of side effects of corticosteroids. As per the medical records, appropriate lifesaving supportive care was not administered and the nursing care was abysmal. The medical records were also not maintained properly.[4]

Thus, in a nutshell, the Courts would in a case of an alleged professional negligence following a cutaneous drug reaction would examine if the right (duly qualified) doctor has prescribed the drug for the correct indication and administered the drug as per accepted professional practices. If the answers to these questions are in the affirmative, there would be no finding of professional negligence on the part of the treating doctor. Thus, the doctor would be held negligent only if there is failure of duty of care toward a patient.

ADVERSE DRUG REACTION AND COUNSELING

While writing a prescription, it is prudent to inform every patient that a drug is known to have side effects and that some side effects could be mild and common and some others could be severe and uncommon. Further, the patient should be asked to stop the medication, if any sign or symptom of a drug allergy occurs (or even on the mere suspicion of a drug allergy) and immediately report to the doctor. Physicians must make it a habit to ask for history of drug allergies and document them prominently in the medical record. This information is useful not only to the doctor at a future date, but also to other treating doctors. It is very important to document because if it is not documented it would be considered to have not been asked. It has been rightly said that "What is documented has been done and what is not documented is not done." Drug interactions increase the risk of adverse drug reactions and hence it is essential that drugs prescribed by other doctors are also noted in the medical records.

Counseling of a patient with a drug allergy and his/her attendants is also important. It should be explained to the patient that drug reaction cannot be predicted and that severe forms of drug reactions are uncommon. Benefit-risk assessment should be communicated to the patient and relatives. The expected course of the drug reaction should also be discussed with the patient and his relatives.

LEARNING ESSENTIALS

- Mere occurrence of a drug reaction does not imply medical negligence.
- Onus of proving negligence lies with the complainant unless 'things speaks for itself'.
- Failure to promptly diagnose or to instruct to stop the incriminating drug or to immediately start appropriate management can lead to liability for medical negligence.
- Appropriate and timely referrals for co-management are important eg, an ophthalmologist, intensivist or physician.
- Documentation in medical records is absolutely essential and this can protect in the event of a litigation.
- Counseling of a patient with drug reaction as well as his/her attendants is very important aspect of management and may help to reduce the chances of litigations.

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Chapter

52

Rare and Interesting Cutaneous Adverse Drug Reactions: Case Snippets

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SUMMARY

Anecdotal experiences and their narration have lost their space in current medical literature. In the life of a clinical dermatologist there are encounters with patients that leave behind an imprint for life. These are random clinical encounters wherein the lesions appeared bizarre, unusual and with very little literature support to recognise them. This chapter is a narration of such experiences, in an attempt to showcase extraordinary cases that failed to get reported in literature. The authors of this chapter have shared them with the hope that readers benefit from such anecdotal experiences and ensure better clinical outcomes.

INTRODUCTION

Interesting patterns of cutaneous or systemic adverse drug reactions are not infrequent in clinical practice. These could be in the form of an eruption with unusual morphological features or at an atypical anatomical location, a commonly occurring rash due to a newer drug, familiar drug causing newer reaction and systemic adverse effects manifesting in various organ systems hitherto unreported.

We present here a compilation of such atypical and rare cases observed in our practice. Knowledge of such reactions is important in clinical decision-making for optimum patient care and could be lifesaving in select instances. Apart from making an interesting reading, general practitioners and academicians alike should find these case snippets immensely useful in real-life situations.

CASE 1: RECURRENT "RECALL REACTIONS" AT SCALD SITES

Case Report

A fifty year old lady presented with extensive bullous lesions, mimicking thermal burns, at the sites of previous scald injury sustained 10 years ago with hot water. Lesions had appeared after she took antispasmodic drug for abdominal pain. The exact identity of drug could not be established as she carried neither the prescription nor the medicine. She had suffered 14 such episodes in 10 years, each time after taking an antispasmodic. Since the lesions were extensive and painful, and since she did not know the exact culprit, challenge was not considered.

Biopsy showed subepidermal bulla and a mixed inflammatory infiltrate. Lesions resolved after a short course of systemic steroid and supportive treatment. It was ironic that nobody had told her about possible association with medicine.

Diagnosis

Antispasmodic drug-induced recall phenomenon at site of previous thermal burns.

Discussion

An interesting concept of "immunocompromised districts (ICD)" has been put forth.[1] According to this, ionizing and UV radiations as well as burns can selectively damage and immunologically mark the area they can act on through direct and indirect mechanisms. The immune behavior is often compromised forever. In recall phenomena, the damaged area usually behaves as an ICD with an exaggerated response to a wide range of drugs (especially chemotherapeutic agents) that prove to be harmless for the undamaged skin.

Chu and Chiu[2] described a patient who developed recall dermatitis on a previously scalded wound, after chemotherapy for acute myeloid leukemia.

Matsuyoshi et al.[3] described development of episodic attacks of burning sensation, purpuric macular eruption, and target-like lesions after taking aspirin and dialuminate for dysmenorrhea, at the site of severe sunburn sustained 8 months earlier.

Our case could also be considered an unusual manifestation of recurrent bullous fixed drug eruption (FDE) due to antispasmodics localizing at previous burn sites. Multiple FDE to minocycline in a patient at sites of previous burn and friction has been reported.[4]

CASE 2: A CASE OF SCABIES, DELIRIUM AND FRACTURES

Case Report

A 30-year-old man having extensive excoriations secondary to scabies was prescribed gamma benzene hexachloride (GBHC) for topical application by his family physician.

He used to sleep on the terrace of his apartment block along with some other inhabitants. On the night of GBHC application, he woke up after midnight highly agitated and rowdy. Other people who woke up, tried to calm him down. He was uncontrollable and jumped from the terrace, sustaining multiple fractures of long bones. He had no prior history of neurological disorder.

Diagnosis

GBHC-induced delirium.

Discussion

Delirium is a serious disturbance of mental abilities resulting in confused thinking and reduced awareness of one's environment. Symptoms tend to be worse at night. Restlessness, agitation, or combative behavior may be part of the manifestations.

Of the applied GBHC, 10% is absorbed through intact skin. Excessive absorption can occur through extensive excoriations, in low-birth-weight babies, prematurely born babies, and in children younger than 2 years as kids have larger skin surface area vis-à-vis body mass. It is a neurotoxin and can cause convulsions. Pregnant and lactating women should also avoid it. Absorption through moist skin can also be substantial. When patients are advised to use GBHC as an antiscabietic, it is advisable to avoid a prior scrub bath (as is usually recommended for routine antiscabetic treatment), avoid vigorous rubbing of skin, and must preferably be applied on dry skin.

Several drugs have been included as deliriants. They include centrally acting agents, analgesics, first-generation antihistamines, antibiotics, cardiac medicines, psychotropic medicines, steroids, etc.[5]

Delirium after GBHC does not appear to have been reported. Neurological adverse effects due to misuse or even proper use of GBHC include seizures, dizziness, headache, paresthesia.[6] Our case reinforces the wisdom of exercising caution when prescribing GBHC lotion specially when safer alternate drugs are available.

CASE 3: FATAL ANAPHYLAXIS AFTER TEST DOSE IN A PATIENT TAKING PENICILLIN INJECTIONS FOR SEVERAL YEARS

Case Report

A 45-year-old staff nurse at the teaching hospital where one of the authors (SP) worked had chronic rheumatic heart disease and recurrent erythema nodosum. She had been taking benzathine penicillin injection at another hospital every month for several years, every time after test dose.

One day, she had anaphylaxis after the test dose; sadly, she could not be resuscitated.

Diagnosis

Penicillin allergy.

Discussion

Erythema nodosum (EN) has been described in acute rheumatic disease[7] but does not seem to be common in chronic rheumatic heart disease. Erythema nodosum can occur in association with several underlying conditions such as microbial infections, rheumatologic diseases, internal malignancies, and adverse drug reactions. Some cases are idiopathic.

The reported incidence of penicillin allergy ranges from 1% to 10% with true incidence of life-threatening anaphylactic reactions ranging between 0.004% and 0.015%.[8]

Since the patient taking penicillin repeatedly can be sensitized to the last exposure, repeat skin testing is recommended before each subsequent course.[9] Some people prefer to carry out scratch testing, followed by intradermal testing.

Skin testing with major and minor determinants of benzyl penicillin is the recommended standard practice. However, a small percentage of patients at risk of anaphylactic reaction will be missed with this testing method.[10] The reliability of using repository

preparation (e.g. benzathine penicillin) for skin testing is questionable.[9]

The present case is a very unusual case in which the patient, who had been taking benzathine penicillin injections for several years, died of anaphylaxis after an intradermal test dose. Deaths due to intradermal, scratch test and even accidental scratch with a needle contaminated with penicillin have been reported though not in the recent past.[11] A case of a 39-year-old woman with rheumatoid arthritis who developed intrapartum anaphylaxis leading to death of the fetus has been published.[12] She had been previously receiving penicillin-based antibiotics without any allergic reactions. As in her case, a subsequent fluorescent enzyme immunoassay revealed a moderate level of specific IgE to penicilloyl G and penicilloyl V, the author suggests that in vitro testing should be undertaken specially in cases in which drug challenge is deemed unsafe. Also any test including skin testing is rarely 100% accurate. Hence some experts feel that even if the patient is negative to the penicillin skin testing, a single oral dose of full-strength penicillin (amoxicillin) should be given immediately after the penicillin testing to practically confirm absence of allergy to the medication after which no further precaution is required.[13]

CASE 4: INTERFERON-ALFA-INDUCED ACUTE EXACERBATION OF PSORIASIS

Case Report

A 45-year-old man, a known case of stable plaque psoriasis (Fig. 52.1 A), had been for some time in a quiescent phase of the disease under good control with topical steroid and antihistamines.

He was recently screened for vague abdominal symptoms of nausea and bloated feeling and on examination was found to have hepatomegaly. Investigations revealed hepatitis C infection. He was started on interferon alfa (IFN-α) and ribavirin therapy.

Within 2 weeks, acute flare-up of psoriasis, with intensely pruritic fresh crops of psoriasis lesions were noted. The above drugs were withheld leading to regression within 2 weeks. However, as his hepatic parameters worsened, the gastroenterologist advised restarting the same drugs to treat his hepatitis C infection leading to exacerbation of psoriasis (Fig. 52.1B). This cyclical flare and remission was noted each time the combination of interferon-α and ribavirin was introduced and withdrawn.

Later only ribavirin was continued for some time during which there was no flare of psoriasis. Restarting IFN-α subsequently induced full blown active psoriasis. As he was a chronic alcoholic,

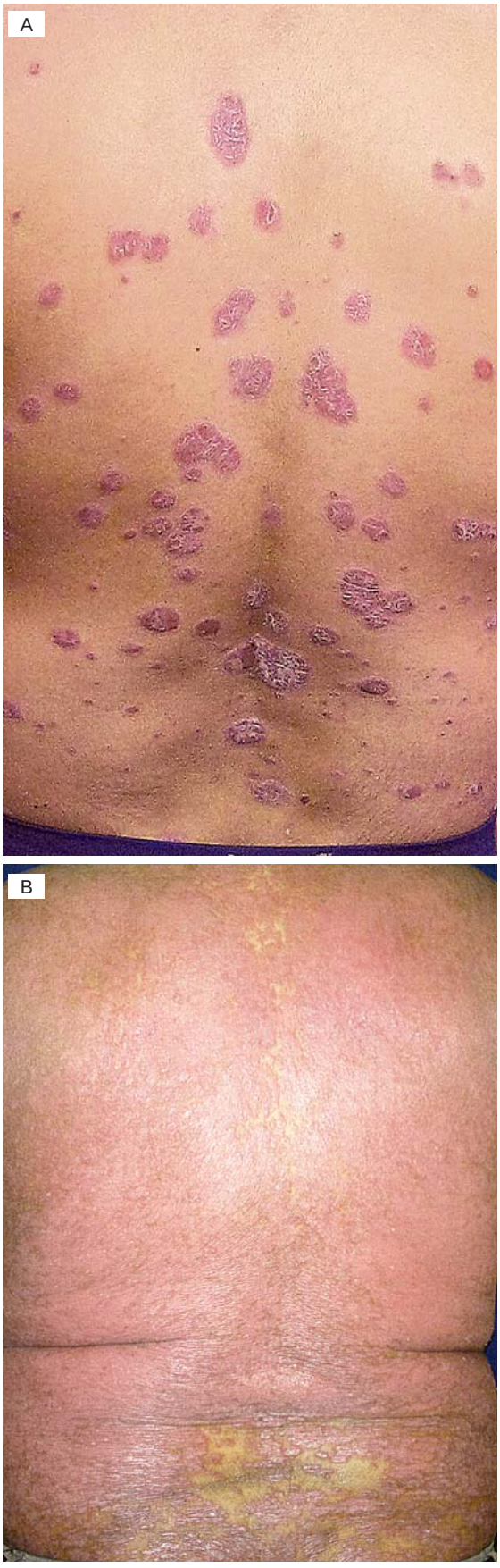

Fig. 52.1: (A) Lesions of stable plaque psoriasis in case 4; (B) Aggravation of psoriatic lesions following interferon therapy for hepatitis C infection.

methotrexate (MTX) was avoided and patient was put on cyclosporine A and phototherapy on different occasions without significant improvement. Borderline hypertension developed after 4 weeks. Remission in psoriasis was only achieved when IFN-α was withdrawn.

Diagnosis

IFN-α-induced acute exacerbation of psoriasis.

Discussion

IFN-α is an immune modulating agent used routinely for treatment of hepatitis B and C infection. Although Neumann had reported its beneficial effects in treatment of psoriasis,[14] its ability to cause induction or exacerbation of psoriasis is being increasingly seen.[15,16] This becomes all the more important in known patients of psoriasis (like our case) who subsequently develop hepatitis C infection where methotrexate and acitretin can cause further hepatic damage.[17] Awareness of such "therapeutic paradox" should guide dermatologists and the internists to use alternate therapies for their patients. Interestingly, etanercept has been used prophylactically to prevent a psoriatic flare in a patient with hepatitis C virus infection treated with IFN-α and ribavirin.[17]

CASE 5: ALLOPURINOL-INDUCED GRANULOMA ANNULARE IN A PATIENT WITH HYDROCHLOROTHIAZIDE-INDUCED GOUT

Case Report

A 40-year-old female patient recently diagnosed as hypertensive was started on oral enalapril and hydrochlorothiazide combination. Six months later she complained of nonspecific joint pains and after investigation was diagnosed as gouty arthtropathy. She was started on allopurinol. Four weeks later, she started to developing lesions typical of granuloma annulare (GA), which was confirmed on biopsy. The lesions did not respond to topical steroids, isotretinoin, and methotrexate and fresh crops of these lesions kept appearing mainly on the face and extremities (Figs. 52.2 A and B).

Her clinical history, literature review, and discussion with physician indicated a possibility of hydrochlorothiazide (uricosuric drug)-induced gout. Withdrawal of allopurinol led to complete regression of cutaneous lesions but aggravated her gout. There was reappearance of GA lesions after restarting allopurinol.

Diagnosis

Allopurinol-induced GA in a case of gout, possibly induced by hydrochlorothiazide.

Discussion

Our case was interesting as drug-induced dermatoses appeared on treating a drug-induced systemic disorder. Had it been suspected, the only action required probably would have been substitution of the offending drug. There are many patients having gout with associated hypertension requiring treatment for both diseases. A tricky situation arises where there is a sudden onset of gout following antihypertensive therapy especially with diuretics, which are known to increase urate levels.[18] The cause of gout due to

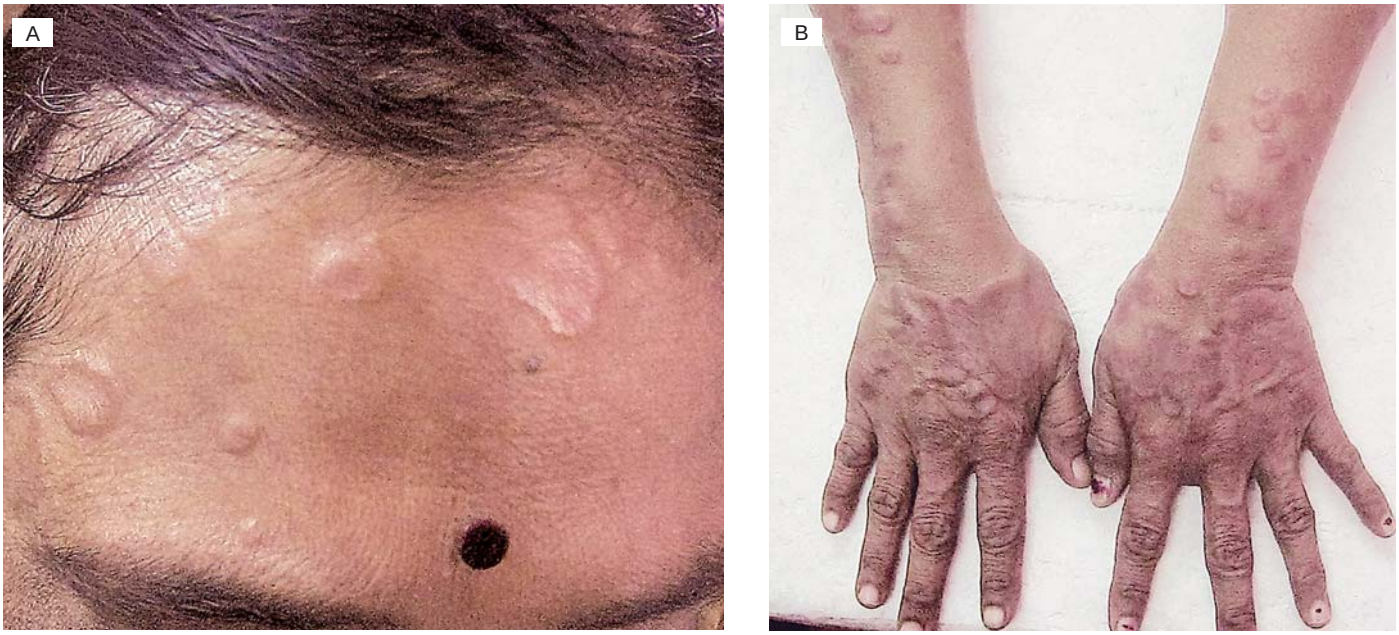

Fig. 52.2: (A & B) Lesions of granuloma annulare on face and upper limbs, following intake of allopurinol for gout.

hydrochlorothiazide in our case was unsuspected and hence it was continued. Even otherwise the decision to stop diuretics, which are cheap and highly effective for hypertension must be individualized, taking into consideration the efficacy and cost of the alternative antihypertensive drug which in addition may be uricosuric-like losartan vis-à-vis adding an independent urate-lowering agent.[19]

Allopurinol is a drug commonly used to treat hyperuricemia. It has also been used to treat granulomatous disorders such as sarcoidosis and even GA.[20] In our case, the appearance and subsequent remission of GA lesions on addition and withdrawal of allopurinol, respectively implicates it as a causative agent, which has rarely been documented in literature.[21]

CASE 6: CHLOROQUINE-INDUCED EXOGENOUS OCHRONOSIS

Case Report

A patient posted in an area with endemicity of malaria was prescribed chloroquine as prophylaxis for malaria.

After some time, he started getting pigmentation on the photo exposed areas (Figs. 52.3 A-C) that was unresponsive to topical steroids and sunscreen. Careful clinical history, examination, and investigations including biopsy, led to a diagnosis of exogenous ochronosis.

Diagnosis

Chloroquine induced exogenous ochronosis.

Discussion

Commonest cause of exogenous ochronosis in Asian setting is probably hydroquinone.[22] Antimalarials such as quinine and quinacrine rarely cause exogenous ochronosis.[23,24] Our patient was on antimalarial prophylaxis with chloroquine, which is known to cause pigmentation on exposed sites as well as oral mucosa on prolonged use.[25] The biopsy findings were characteristic of ochronosis. Ochronosis should be suspected in patients on antimalarial agents such as chloroquine which is commonly used drug in dermatology practice.

CASE 7: TOXIC EPIDERMAL NECROLYSIS–LIKE ERUPTION FACILITATED BY CHIKUNGUNYA

Case Report

In 2006, Gujarat along with many states of India witnessed epidemic of chikungunya. Unusual cutaneous eruptions including cutaneous adverse drug reactions (CADRs) were observed in this immunity lowering viral attack.

Six cases, mainly infants and neonates, presented to pediatrician for high-grade fever without significant joint pains. Their mothers suffered from viral arthritis. All developed clear or occasional hemorrhagic vesiculobullous lesions within 2–4 days of administration of intravenous aminopenicillins/cephalosporins. The eruptions were toxic epidermal necrolysis (TEN) like and mainly on trunk and limbs. CD4:CD8 ratio was reversed in four out of six samples studied. The cutaneous lesions increased

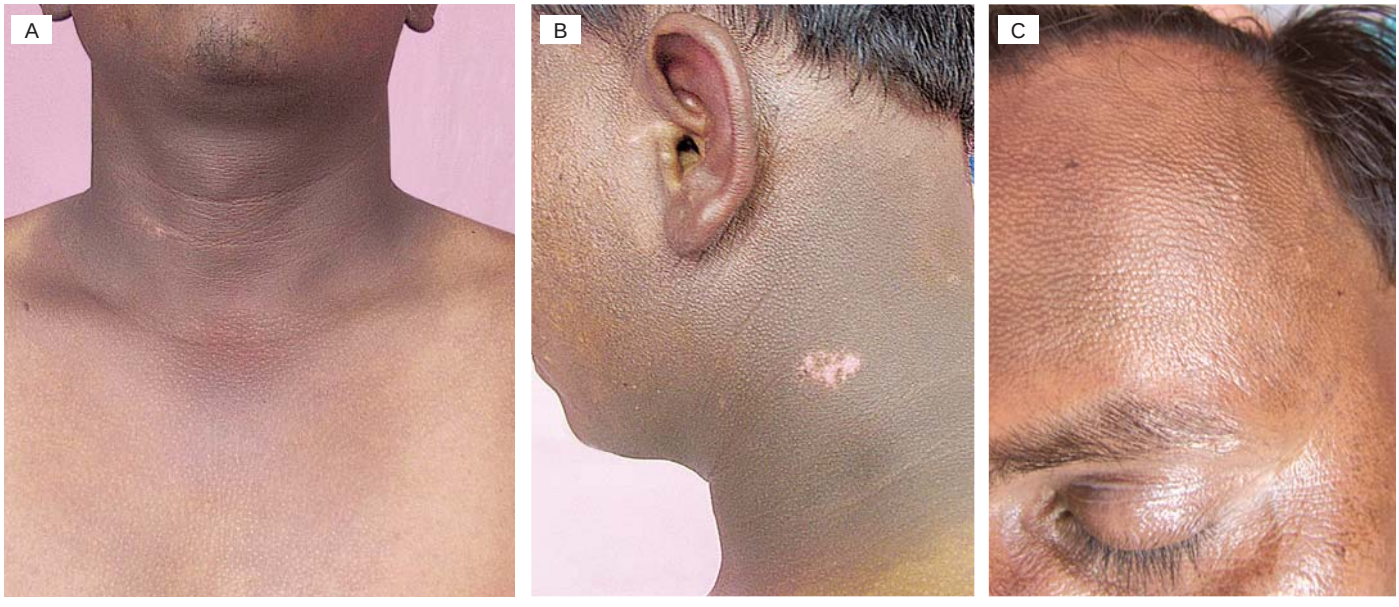

Fig. 52.3: (A–C) Chloroquine induced exogenous ochronosis developing in a patient on chloroquine prophylaxis of malaria.

for 3–4 days following withdrawal of the drugs and healed spontaneously without scarring within 5–7 days, leaving scaling and occasional erythema. The outcome was uneventful in all cases.

A young male patient suffering from high-grade fever, confirmed to be due to chikungunya, presented with necrotic TEN like lesions and progressive generalized sheet like exfoliation of the skin (Figs. 52.4 A and B), 5 days after administration of second-generation cephalosporins. There was no involvement of the oral mucosa and he did not appear toxic. He had low WBC and low platelet during active infection. The erosions rapidly healed within 10 days of withdrawal of the drug. A short 7-day course of cyclosporin along with supportive therapy was given during this period.

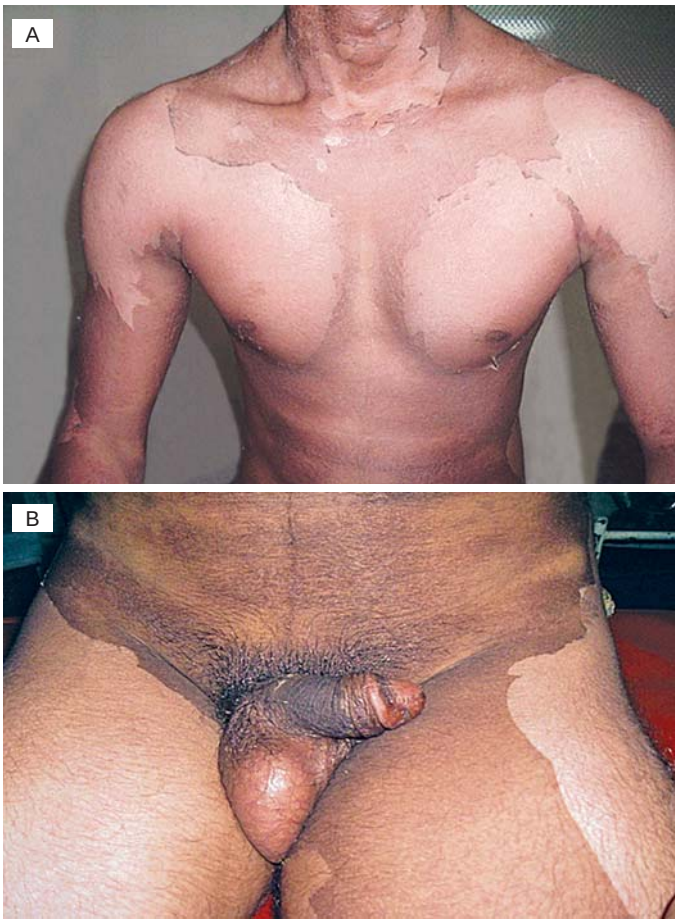

Fig. 52.4: (A & B) Cephalosporin-induced TEN-like eruptions in a young male facilitated by chikungunya.

Diagnosis

Drug-induced TEN-like eruptions facilitated by chikungunya.

Discussion

TEN-like eruptions are classically drug induced though rarely infective causes like *Mycoplasma* have been described.[26] The Indian subcontinent has, of late, encountered annual epidemics of chikungunya in various states and several cutaneous manifestations have been reported.[27] TEN-like eruptions may occur during a course of chikungunya in certain patients, specially infants. The absence of oral lesions and rapid resolution are points of differentiation from actual TEN. It is also known that a spectrum of adverse drug reactions can be caused by the combined action of drugs and viruses viz. ampicillin rash in acute infectious mononucleosis; Reye's syndrome, hypersensitivity reactions to sulfonamides in patients with HIV infection.[28] It is possible that viral infections are acting as costimulators for an ultimate drug–T-cell receptor (TCR) interaction, which results in clinical manifestation of reaction. An efficient stimulation of T cells by a drug is the sum of drug–TCR affinity and "readiness" of the cell to react. If the immune system is resting, only drug–TCR interactions of high affinity may be able to stimulate T cells sufficiently to cause T-cell expansion. If the immune system is already activated by a prior or coexisting viral infection, the readiness of cells to react is increased (lower threshold). Thus even drug–TCR interactions of relatively low affinity will be enough to activate many T cells, thus resulting in a symptomatic reaction. This implies that when the costimulatory conditions are no longer present, the same drug will be later well tolerated.[29] The possibility of viral drug host interaction is to considered in such presentations. clinical picture gets modified wit the viral affection of skin. Further, drug metabolism and host immune response are modified by the viral infection to result in bizzare presentations.

CASE 8: BULLOUS PEMPHIGOID DUE TO GLIPTINS

Case Report

A 75-year-old man with hypertension, diabetes, and dyslipidemia presented with vesiculobullous lesions for the past 2 years (Fig. 52.5). Biopsy confirmed bullous pemphigoid (BP). There was no evidence of other coexisting systemic autoimmune disorders. His diabetes worsened following administration of high doses of steroid and immunosuppressive drugs.

On reviewing his endocrinologist's treatment records, it was observed that his skin lesions had started 4 weeks after starting vildagliptin belonging to a group of medicines called dipeptidyl peptidase-4 inhibitors used to treat patients with diabetes mellitus. Prior to this he had been on metformin, which did not help in controlling his diabetes. Complete remission of skin lesions occurred after withdrawing vildagliptin.

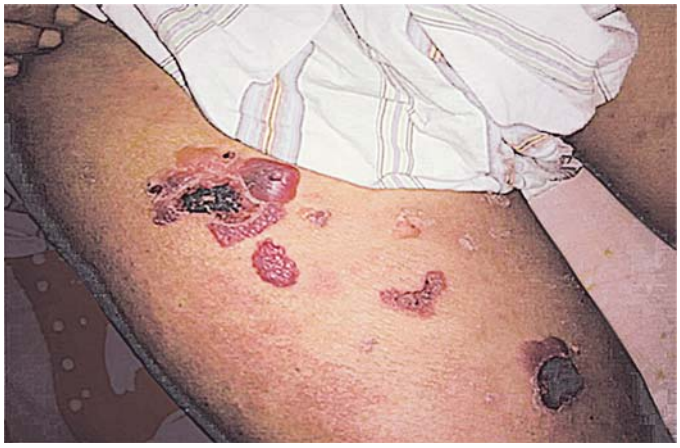

Fig. 52.5: Vildagliptin-induced bullous pemphigoid lesions in an elderly male.

Diagnosis

Vildagliptin-induced BP.

Discussion

"Gliptins" is the nickname given to a group of medicines called dipeptidyl peptidase-4 inhibitors. Sitagliptin, vildagliptin, saxagliptin, linagliptin are some of the examples of gliptins. Reports of BP occurring few weeks to several months after administration of oral hypoglycemic agents particularly vildagliptin has been reported.[30,31] This has important implications as idiopathic BP is usually treated with systemic corticosteroids, which could complicate the management of diabetes. Therefore, it is important to suspect the diagnosis of drug-induced BP early and withdraw the offending drug quickly to avoid aggravating diabetes and its potential morbidity.

CASE 9: ABDOMINAL COLIC AFTER APPLICATION OF TOPICAL CLINDAMYCIN

Case Report

A 21-year-old male patient on treatment of acne with topical clindamycin lotion since 3 weeks presented with sudden onset of abdominal colic. As there was no other apparent cause of his abdominal symptom, topical clindamycin was suspected to be the possible reason. Symptoms of colicky pain completely subsided after withdrawal of topical clindamycin. Rechallenge with topical clindamycin led to repetition of abdominal colic within few hours after topical application.

Another 16-year-old female patient of acne reported diarrhea following 8–9 days of application of topical clindamycin gel. It also subsided on withdrawal of the topical medication.

Diagnosis

Clindamycin-induced gastrointestinal (GI) symptoms.

Discussion

Clindamycin is a very commonly used drug by dermatologist for acne and other dermatosis. Awareness of these important adverse effects due to clindamycin[32,33] will ensure that new drug therapy is not started for GI upset but clindamycin is withdrawn. Occurrence of serious adverse effects with topical medication for acne is an important lesson to be learnt here.

CASE 10: IMATINIB-INDUCED HAND–FOOT SYNDROME

Imatinib mesylate is a potent inhibitor of protein kinases such as c-Kit. It is used to treat various malignancies such as gastrointestinal stromal tumor (GIST), acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML). Hand–foot syndrome (HFS) is rarely reported with imatinib. The authors came across two cases of HFS with imatinib.

Case 10 A

A 45-year-old woman newly diagnosed as a case of GIST, positive for c-Kit mutation and vimentin, was started on tab imatinib 400 mg OD and other supportive. Within 45 days of starting the therapy, she presented with the complaints of burning pain over palms and soles followed by appearance of skin lesions. Examination revealed multiple, erythematous, discrete, infiltrative, extremely tender, nonpruritic nodules on palms and soles (Figs. 52.6 A and B). The patient was clinically stable with no other skin complaints.

She discontinued the therapy on her own due to extreme discomfort. Healing with desquamation of skin and resolution of nodules and pain was observed after a week of stopping the drug and starting symptomatic treatment for her skin lesions The drug had to be restarted because of advancing underlying disease. This time lesions reappeared involving even the knee within 1 week of starting imatinib in the same dose.

Case 10 B

A 40-year-old woman diagnosed as a case of chronic myelogenous leukemia was initially put on hydroxyurea for 6 months. She was later shifted to oral imatinib 400 mg/day. The dose of imatinib was increased to 600 mg/day and later to 800 mg/day. Multiple erythematous, tender papulonodular lesions appeared on palms and soles after 2 months of increasing the dose (Figs. 52.7 A and B).

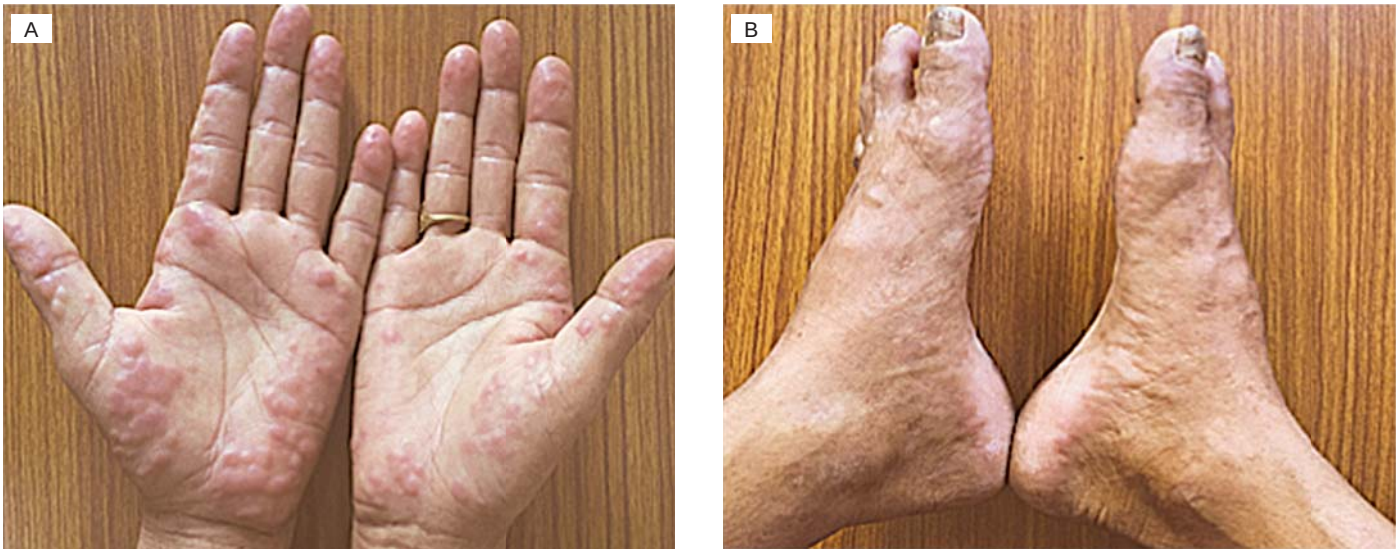

Fig. 52.6 (Case 10 A): (A & B) Tender nodular lesions on palms and soles following imatinib treatment for gastrointestinal stromal tumor.

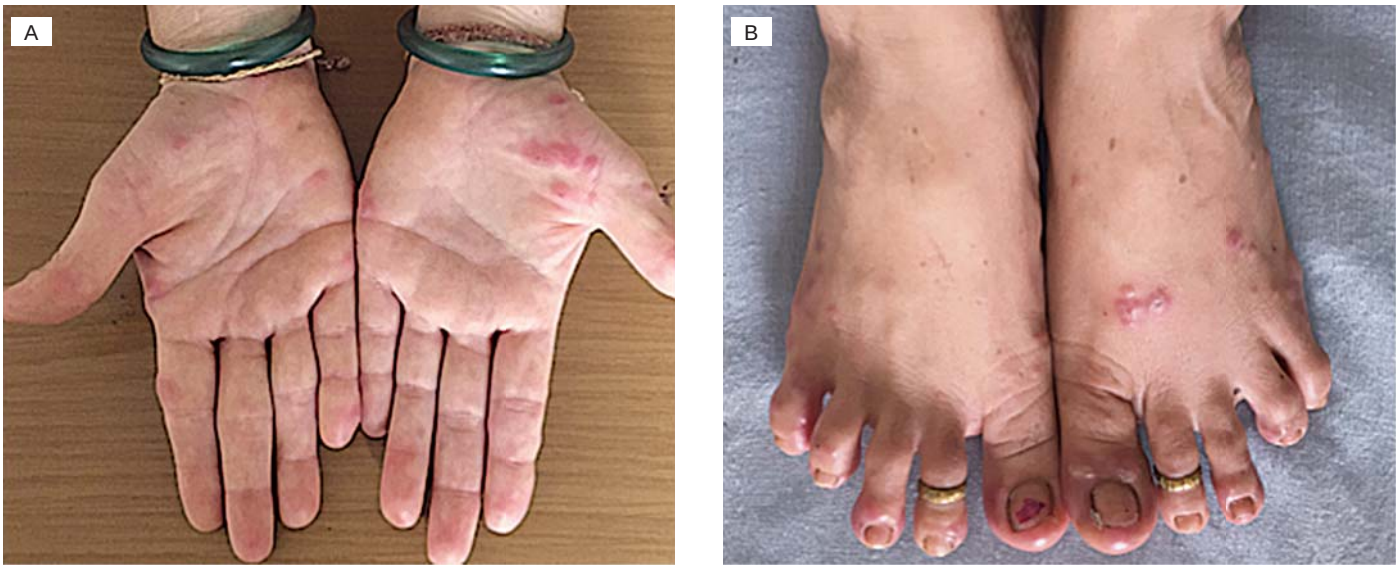

Fig. 52.7 (Case 10 B): (A & B) Tender nodules on hands and feet, developing in a patient receiving imatinib treatment for chronic myeloid leukemia.

The skin biopsy in these patients revealed a hyperplastic squamous epithelium with hyperkeratosis, epidermis with multiple intraepidermal vesicles, reticular degeneration at the dermoepidermal junction, mild inflammation in dermis, and mild perivascular lymphocytic infiltrate with occasional neutrophils (Figs. 52. 8 A and B).

The reaction was categorized as "certain" using the World Health Organization Uppsala Monitoring Centre (WHO-UMC) causality criteria. Both these patients were successfully treated with oral prednisolone 20 mg/day for 1 week followed by 10 mg/day daily for another 1 week along with emollients. Avoidance of friction of palms and soles and cold compresses helped symptomatically.

Diagnosis

Imatinib-induced hand foot syndrome.

Discussion

HFS, also known as palmoplantar erythrodysesthesia (PPE), is a distinctive CADR to certain chemotherapeutic agents. It is caused by drugs after they are excreted through the eccrine duct. Palms and soles have high density of eccrine glands, thus are commonly affected as observed in our two cases. Clinically, it is characterized by painful symmetric erythema, papulonodules, or blisters localized to areas of increased pressure on the hands and feet.[34] Painful hyperkeratosis and desquamation may occur. The common culprits are 5-fluorouracil, capecitabine,

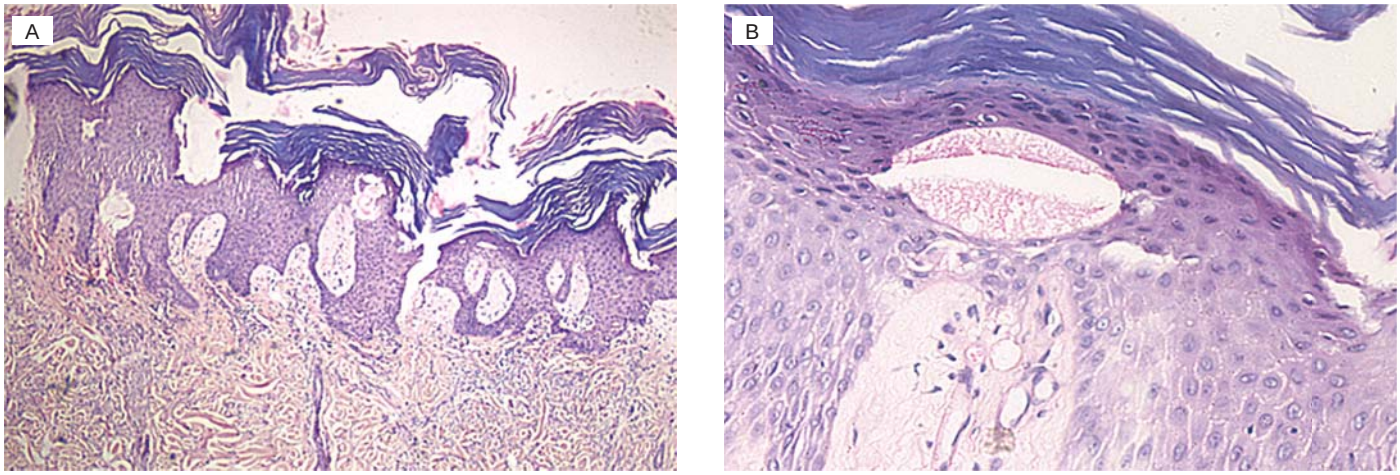

Fig. 52.8: (A & B) Histopathology (H&E; 10X, 40X) in case 10 B, showing hyperplastic squamous epithelium, intraepidermal vesicle and mild perivascular lymphohistiocytic infiltrate.

cytarabine, docetaxel, and doxorubicin. Imatinib is frequently known to cause side effects such as maculopapular rash, pityriasis rosea–like lesions, skin hypopigmentation, acute generalized exanthematous pustulosis, exacerbation of psoriasis, pseudoporphyria, and mycosis fungoides–like reaction. HFS with imatinib is rare.[35] Therefore, a high degree of clinical suspicion is required on the part of a physician to diagnose HFS and such unusual reactions need to be reported.

CASE 11: TOPICAL STEROID INDUCED COUGH PURPURA ON THE FACE

Case Report

A 22 year old nurse presented with sudden shower of purpuric eruptions on her face after a bout of violent cough, during an acute attack of fever and pharyngitis. On detailed history, this young lady had been applying topical betamethasone cream for itching on the face (undiagnosed lesions) for over 2 years as an over the counter self medication,. She had been on follow up with the author for over a month in an attempt to wean her out of the topical steroid dependency. During this time she developed an incessant cough early in the morning following which she noticed reddish raised spots on the entire face. She had no other comorbidities or co medications.

On examination, she was noted to have petechiae scattered across the face with lesions predominant on the cheeks, mandibular area and forehead (Fig. 52.9 A). Closer examination with a hand lens showed multiple telangiectasia on a background of a papery white atrophic thinned out skin (Fig. 52.9 B.)

She refused histopathologic examination.

Diagnosis

Topical Steroid induced Cough Purpura on the face.

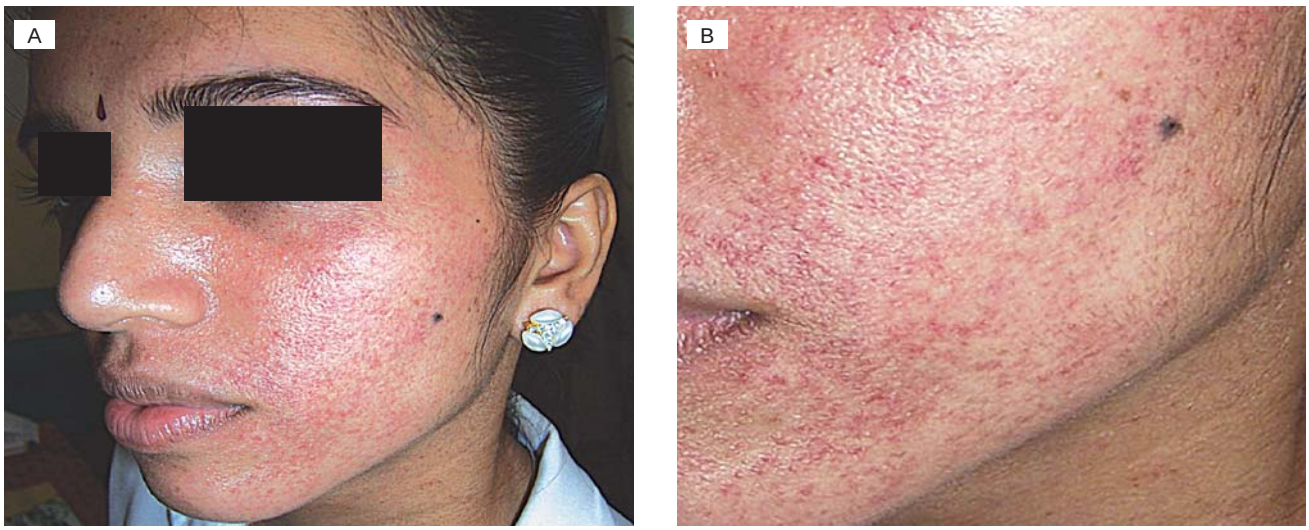

Fig. 52.9: Cough purpura in TSDF (A); Closer view of the same patient (B).

Discussion

Clinically the sequence of events could be summarized as follows. Patient had a chronic itch on the face for which topical steroid was applied as self medication (repurchased by her as over the counter from a local pharmacy without prescription). The chronic topical steroid use caused thinning, atrophy, telangiectasia and hypopigmentation. The thinned out blood vessels were prone to easy bruisability and breakage due to steroid induced collagen synthesis inhibition. The bout of cough caused a sudden breakage of the blood vessels which resulted in the shower of purpuric eruptions.

While cough purpura is a reported entity, the regional distribution on the face in this case is attributable to the chronic topical steroid abuse- an entity described as topical steroid damaged face or TSDF. While spontaneous purpura occurring at sites of steroid application is reported, cough purpura is hitherto unreported .

CASE 12: PENTAZOCINE INDUCED IRRITANT REACTION WITH CONTACT PIGMENTATION LIP

Case Report

A 23 year old nurse was assigned to the labour room for night duty and was ordered by the duty obstetrician to administer Inj pentazocine to a patient who had severe pain post operatively after caesarean section. She opened the vial of Inj pentazocine, in panic, by breaking the vial with her teeth instead of breaking it with a vial opener blade. The contact of pentazocine solution with the lip produced an immediate epidermal necrosis of the skin of the lower lip leaving behind an erythematous circular area with a central pigmentation (Fig. 52.10). She immediately washed off the liquid when she felt a burning sensation at the site thus sparing spread of the irritant reaction. The appearance of the lesion resembled a FDE and a differential diagnosis was considered. There was no history of fever or intake of food, coloring agents or medications that could have precipitated an FDE reaction.

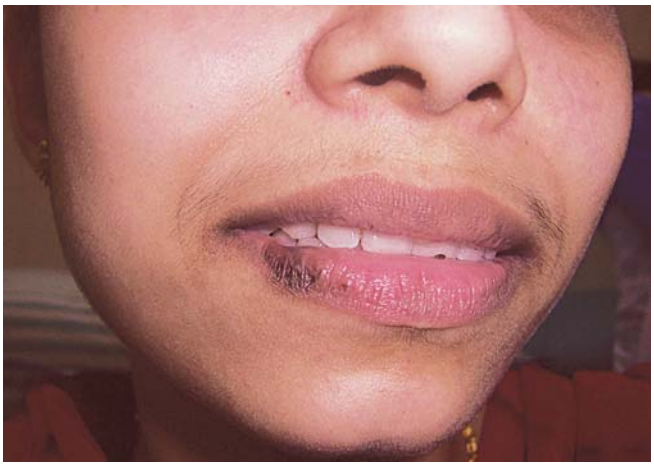

Fig. 52.10: Contact pigmentation and irritant reaction to pentazocine.

Diagnosis

Contact pigmentation and irritant reaction to pentazocine.

Discussion

Pentazocine is an irritant substance that can cause necrotic irritant reactions when administered parenterally for analgesia. However, this case is unique as the nurse inadvertently came in contact with the liquid while attempting to open the vial with her teeth.

CASE 13: IMATINIB INDUCED VASCULITIS

Case Report

A 65 year old gentleman who was diagnosed to have gastrointestinal stromal tumour was started on imatinib mesylate as treatment for the disease. He developed multiple erythematous and violaceous papular eruptions on the legs bilaterally which were initially asymptomatic and later became painful. The lesions had a violaceous hue (Fig. 52.11 A) and hence a clinical possibility of lichenoid drug reaction was considered. Histopathology was done to confirm the diagnosis. The lesions responded to oral corticosteroids (Fig. 52.11 B).

Histopathology revealed features of leukocytoclastic vasculitis with fibrinoid necrosis and RBC extravasation.

Diagnosis

Imatinib induced vasculitis.

Discussion

Imatinib is the prototype of the targeted therapy drugs used in oncology. It is used to treat several diseases like Philadelphia Positive Chronic Myeloid Leukemia (Ph+ CML), Philadelphia Positive Acute lymphoblastic lymphoma (Ph+ALL), Gastrointestinal stromal tumour (GIST), Myelodysplastic syndrome (MDS) and Aggressive Systemic mastocytosis (ASM). It produces a variety of adverse effects which include cutaneous ADRs like pruritic maculopapular exanthem, follicular mucinosis, erythroderma, graft-versus-host-like-disease, mycosis fungoides-like reaction, small vessels vasculitis, generalized exanthematous

pustulosis, Stevens-Johnson syndrome, pityriasis rosea-like eruption, Sweet syndrome, edema, and lichenoid eruption ;hyperpigmentation of skin nails and teeth have been extensively studied.[36]

Purpuric vasculitis has been reported by Hamm et al.[37] However this presentation in the form of a lichenoid -like clinical morphology with a vasculitis-like histology is unreported, to the best of the author's knowledge and underlines the importance of histopathologic examination in diagnosis of clinical presentations that appear apparently usual.

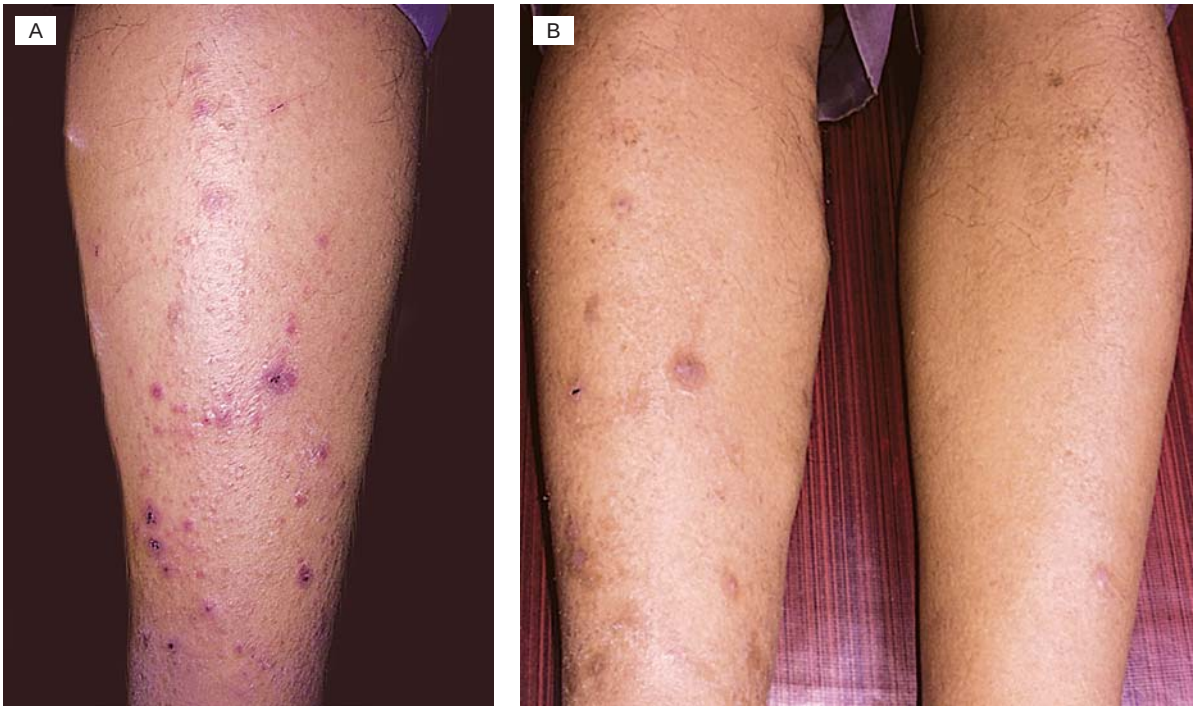

Fig. 52.11: Imatinib induced vasculitis on legs (A); same patient post steroid treatment (B).

LEARNING ESSENTIALS

- The interesting cases presented here serve to reemphasize that adverse drug reaction can present in various cutaneous and systemic forms and can never be considered as a trivial matter.
- Recognizing them in time can not only be lifesaving but would save the patient from being overtreated by drugs for drug-induced illnesses, which would otherwise require a simple withdrawal of the offending agent.
- A constant vigil on the part of treating physician would help to unravel uncommon and even unknown adverse drug reactions thus strengthening the pharmacovigilance.

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Section VI: Appendix

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Appendix 1

Patient Information Sheet on Adverse Drug Reactions

Q. 1 What is an adverse drug reaction (ADR)?

Ans. An unwanted or harmful reaction that develops in patients while they are taking a medicine or combination of medicines.

Q. 2 Can ADRs be serious?

Ans. Most of the ADRs are mild, not bothersome, and do not generally require a change in therapy. A few, however, can be serious, disabling or life-threatening and may require immediate stoppage of treatment and hospitalization.

Q. 3 Who are likely to develop an ADR?

Ans. Any one can develop an ADR but certain groups such as the elderly patients on multiple drugs, those with a previous or family history of drug reaction, HIV-positive individuals and patients with liver and kidney failure are at higher risk.

Q. 4 What are the common signs and symptoms of an ADR?

Ans. Though an ADR can mimic any skin disease, the most common symptoms are itching or development of a rash on skin, lips or inside mouth after starting the drug. Many a times, such symptoms may suddenly appear after prolonged use of a particular drug. An ADR may also present as swelling of face and lips with difficulty in breathing. Blister or pain in skin may also be a warning sign of a drug reaction. Once a person develops a reaction, he/she is likely to develop a subsequent reaction of greater severity in the event of readministration of the suspected drug again.

Q. 5 Which drugs are most likely to cause ADRs?

Ans. No drug is absolutely safe and any drug can cause reaction but certain drug groups such as antibiotics, antiepileptics, and pain killers are more liable to cause reactions. Sometimes, a drug itself may not cause an ADR but on taking with another drug, there could be an interaction leading to an ADR.

Q. 5 Can ADRs be predicted?

Ans. No, one cannot always predict the ADRs except a few that are related to the overdose of a particular drug. Some of the ADRs occur after prolonged use of a drug. It can develop even after stoppage of the drug.

Q. 6 Are home remedies, over-the-counter (OTC) products, homeopathic, ayurvedic, and alternative medications absolutely safe?

Ans. No, this is a great myth. No medicine is absolutely safe. One can develop reaction to any of these. One can develop adverse reaction even to locally applied medications such as steroids and fairness creams, available OTC.

Q. 7 Is ADR due to negligence of your doctor?

Ans. Absolutely not. A drug reaction is not a mistake of the treating doctor or result of his negligence. It is merely a matter of chance. Anyone can react to any drug. Reactions to medication(s) occur due to the unique genetic makeup of a person, which makes him/her more prone to a particular drug reaction. A drug causing ADR in one person does not necessarily produce reaction in other persons.

Q 8 What should I do in case of drug reaction?

Ans. In the event of drug reaction, do not panic. Most reactions are generally self-limiting and subside promptly on withdrawal of offending drug(s). Report immediately to your treating physician or nearby physician available. Carry your complete medical record along with the strips, wrappers, boxes of medication consumed by

you. This will help your doctor in identifying the suspected drug(s) and prevent reaction in future. Avoid the suspected and related drug(s) as instructed by your physician, in future.

Q. 9 How can ADRs be prevented?

Ans.

- Avoid taking drugs for minor ailments as far as possible.
- Do not self-medicate for minor ailments even with topical medications. It could be dangerous.
- Take medicines only in consultation with qualified doctor. Avoid seeking consultations from quacks, chemists, friends/relatives, traditional faith healers, or unqualified practitioner.
- Follow your doctor's instructions strictly. Do not increase the dose or extend the treatment on your own.
- Always inform your physician about the history of reaction to drug(s) in you or your family members and carry the list of suspected drugs/ADR card in your purse or handbag and show it to the treating doctor every time you visit them.
- Strictly avoid the suspected drug(s) in future. One has to avoid all the chemically related suspected drugs as suggested by the doctor.
- Do not panic or blame your doctor for the drug reaction. Stop the suspected drug and contact your doctor immediately and follow their instructions.

Appendix 2

Cutaneous Adverse Drug Reaction Recording Proforma (Prepared by IADVL's Special Interest Group on Adverse Drug Reactions)

General information **Centre code & place:** ☐ ☐

Name: ☐ Age/sex: ☐ ☐ Weight (kg): ☐

Occupation: ☐ Phone no: ☐

Address: ☐

Suspected drug(s): ☐

Primary illness prompting drug intake: ☐

History of drug reaction in past: Yes ☐ No ☐ Nature: ☐

Interval between drug intake and onset of rash: <24 hour ☐ 1-3 days ☐ 3–7 days ☐ 1–3 weeks ☐ >3 weeks ☐

Interval between onset of rash and presentation: <24 hours ☐ 1-3 days ☐ 3–7 days ☐ 1–3 weeks ☐ >3 weeks ☐

Symptom: Itch ☐ Burning ☐ Pain ☐ Asymptomatic ☐

Comorbidities: DM ☐ HTN ☐ Malignancy ☐ CAD ☐ CKD ☐ Connective tissue disorder ☐ Psychiatric illness ☐ HIV ☐

HSV infection ☐ Pregnant ☐ Lactating ☐ Immunosuppressive therapy ☐ Others ☐

Nature of rash: Serious (SCAR*) ☐ Nonserious ☐

Pattern of rash: MPR ☐ FDE ☐ Urticaria ☐ Angioedema ☐ Lichenoid ☐ Psoriasiform ☐ Acneiform ☐ DHS ☐ EM ☐ SJS ☐

SJS/TEN ☐ TEN ☐ Erythroderma ☐ AGEP ☐ Eczematous ☐ Bullous ☐ Purpuric ☐ Other ☐

FDE

Morphology: Macular ☐ Bullous ☐ Both ☐
Nonpigmented ☐ Giant ☐ Eczematous ☐ Linear ☐ Urticarial ☐ Psoriasiform ☐ other ☐

Site(s): Cutaneous ☐ Mucosal ☐ Both ☐

Cutaneous: Face ☐ Neck ☐ Back ☐ Abdomen ☐ Buttocks ☐ Genitals ☐ Upper limb ☐ Lower limb ☐

Mucosal: Lips ☐ Genitals ☐ Anal ☐ Nasal ☐ Others ☐

Number of lesion(s): 1 ☐ 2-5 ☐ 5-10 ☐ >10 ☐

Size: <1 cm (no.) ☐ 1–5 cm (no.) ☐ >5 cm (no.) ☐

Episode of FDE: I ☐ /II ☐ /III ☐ /IV ☐ /V ☐ /VI ☐

New lesion(s) in the current episode: yes ☐ no ☐

Oral provocation: Positive ☐ Negative ☐ Not done ☐

Patch test: Not done ☐ Done ☐ Positive: Lesional ☐ Normal skin ☐ Both ☐ Negative ☐

Diagnosis: SJS ☐ SJS-TEN ☐ TEN ☐ DHS ☐ /AGEP ☐ Erythroderma ☐ Anaphylaxis ☐ Others: ☐

Skin involvement (BSA): <10% ☐ 10%–20% ☐ 20%–30% ☐ 30%–50% ☐ >50% ☐

Mucosal involvements: Sites: Ocular ☐ Nasal ☐ Oral ☐ Genital ☐ Anal ☐ Others ☐

Severity: Mild ☐ Moderate ☐ Severe ☐

Lesion(s) morphology: Macules ☐ Papules ☐ Maculopapular ☐ Purpuric ☐ Ecchymosis ☐ Vesiculobullous ☐
Pustules ☐ Erosions ☐ Target lesions ☐ others ☐

Associated systemic symptoms: Fever ☐ Joint pain ☐ Lymphadenopathy ☐ Hepatomegaly ☐ Splenomegaly ☐
Facial edema ☐ Others: ☐

Vitals (At the time of admission): Pulse ☐ BP ☐ Resp. Rate ☐ Temperature ☐

SCORTEN: ☐

Drug details (in order of suspicion)	S. No	Name of drugs ☐ ☐ ☐	Dose used ☐	Route	Frequency	Date started	Date stopped	Reason for use
	1							
	2							
	3							
	4							
	5							

Effect of withdrawal		Reduced ☐ no change ☐ unknown ☐ NA ☐	**Investigations:** Anemia ☐ Eosinophilia ☐ Leukocytosis ☐ Leukopenia ☐ Thrombocytopenia ☐ ↑Liver enz ☐ ↑B. urea ☐ ↑S. Creatinine ☐ Blood sugar ☐ Bicarbonates ☐ Others ☐					
Effect of reintroduction		Aggravation ☐ no change ☐ unknown ☐ NA ☐						
Concomitant medicine (alternatives/ herbal?		No ☐ Yes ☐ Details _____	Biopsy ☐					
Treatment provided	S. No	Name of drugs	Dose used	Route	Frequency	Date started	Response	Comments
	1							
	2							
	3							
	4							
	5							

FINAL OUTCOME: Recovered ☐ Died ☐ Disabled ☐

CAUSAL ASSESSMENT: Certain ☐ Probable ☐ Doubtful ☐

Additional/Final Remarks by the Investigator ☐

Certain: Rash occurs in plausible time relation to drug intake; can't be explained by concurrent ds./drug(s); plausible response to withdrawal and rechallenge (if done).

Probable: Reasonable time relation to drug intake; unlikely attributable to other ds./drug(s); reasonable response to withdrawal; rechallenge not required.

Possible: Reasonable time relation to drug intake; could also be explained by other concurrent ds./drug(s); drug withdrawal information lacking/unclear.

SCAR (Severe Cutaneous Drug Reaction): Rash resulting in serious skin damage/involve multiple organs/requires hospitalization or prolongs hospital stay/cause significant morbidity, death.

Appendix 3A

ADR Reporting Pharmacovigilance Programme of India and Mobile Applications

The Pharmacovigilance Programme of India (PvPI) is a nation-wide pharmacovigilance program initiated by the Central Drugs Standard Control Organization (CDSCO), New Delhi, under the aegis of Ministry of Health and Family Welfare, Government of India. The program was started in July 2010 with the All India Institute of Medical Sciences (AIIMS), New Delhi as the National Coordinating Centre (NCC) for monitoring Adverse Drug Reactions (ADR) in the country to safe-guard Public Health. The NCC was then shifted to the Indian Pharmacopoeia Commission (IPC), Ghaziabad, (Uttar Pradesh) in April 2011. Twenty two ADR monitoring centres (AMCs) including AIIMS, New Delhi have been set up under this Program and they forward ADR data to the NCC at PvPI.

"The purpose of the PvPI is to collate data, analyze it and use the inferences to recommend informed regulatory interventions, besides communicating risks to healthcare professionals and the public. The broadened patient safety scope of pharmacovigilance includes the detection of medicines of substandard quality as well as prescribing, dispensing and administration errors". (Source: PvPI website.)

HOW ARE ADVERSE REACTIONS REPORTED?

If there is any suspicion that an adverse event or adverse reaction has occurred, the health-care professional attending to the patient, can fill up the suspected ADR form and forward it to the AMC. Also, if a patient suspects that he has experienced an ADR he can report to the nearest AMCs or call the AMC for advice. This is called an Individual Case Safety Report (ICSR). ICSRs are reported from all over the country from the regional AMCs to NCC-PvPI. This information is then forwarded through the Vigibase software to the WHO-UMC monitoring centre at Uppsala, Sweden which maintains the global database of ADRs. The center then generates signal detection and Black box warnings for safe usage of drugs. The route map for ADR reporting is summarized in Fig. 1.

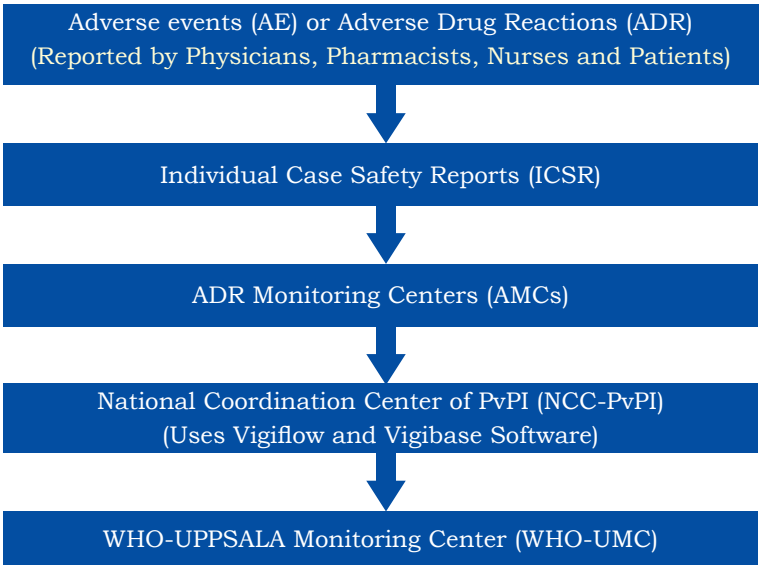

Fig. 1: Route map for reporting ADRs in India.

NCC-PvPI monitors the ADRs among Indian population and helps the regulatory authority of India (CDSCO) in taking decision on safe use of medicines. The ICSRs are collected/collated in a scientific way and analyzed to facilitate appropriate decisions at CDSCO.

Who Can Report?

All health-care professionals including Clinicians, Dentists, Pharmacists, Nurses and Non-health-care professionals (patients, consumers) can report ADRs.

A helpline number 1800 180 3024 (All working days 9:00 AM to 5:30PM) managed by NCC-PvPI is available to provide assistance in ADRs reporting for the HCPs and general public. More details can be obtained at the PvPI website: www.ipc.gov.in/PvPI/.

Mobile App for ADR Reporting

Mobile applications have revolutionized the way data are managed in scientific circles. To ensure quick and confidential reporting, PvPI has initiated a mobile app service. The "ADR reporting app", is a smart phone application for android users, conceived by Dr. Sachin Kuchya, (Associate Professor in Pharmacology at NSCB Medical College, Jabalpur, Madhya Pradesh, India) and developed in collaboration with IPC, National Coordination Centre, PvPI (NCC-PvPI), Ghaziabad (Uttar Pradesh, India). With the help of ADR reporting app, Physicians–Nurses–Pharmacists, can instantly report any suspected Adverse Drug Reaction, to NCC-PvPI, from all over India.

This app can be accessed on Google play store at the following link:

https://play.google.com/store/apps/details?id=sADRReporting.sADRReporting&hl=en

Features of the Mobile App

1. Is customized for reporter, the reporter information needs to be filled only once.
2. Has auto-entry, a drug once reported goes into database and gets displayed upon next reporting.
3. ADR's due to fixed drug combinations can be reported with a single entry regarding their, dosage regimen, labeling details and indications.
4. Paperless and instantaneous submission.
5. Algorithm-based causality assessment, based on WHO criteria.
6. Option to choose nearest or preferred AMC.
7. Incentive to reporter—An autogenerated copy of duly filled suspected ADR form as .pdf file, is sent as acknowledgement to the reporter's email account, for his record, review & research purpose.
8. A thorough confidentiality is maintained. Program staff is not expected to and will not disclose the reporter's identity in response to a request from the public. Submission of a report does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the reaction.

   Other countries have similar apps (United Kingdom—Yellow card, Netherlands—LAREB, Croatia—HALMED) and are accessible with the following link:

   https://web-radr.eu/mobile-applications-for-adr-submission/

Appendix 3B

Version-1.2

SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

For VOLUNTARY reporting of Adverse Drug Reactions by Healthcare Professionals

INDIAN PHARMACOPOEIA COMMISSION
(National Coordination Centre-Pharmacovigilance Programme of India)
Ministry of Health & Family Welfare, Government of India
Sector-23, Raj Nagar, Ghaziabad-201002

FOR AMC/NCC USE ONLY

AMC Report No. :

Report Type ☐ Initial ☐ Follow up

Worldwide Unique No. :

A. PATIENT INFORMATION

1. Patient Initials _____

2. Age at time of Event or Date of Birth _____

3. M ☐ F ☐ Other ☐

4. Weight_____Kgs

12. Relevant tests/ laboratory data with dates

B. SUSPECTED ADVERSE REACTION

5. Date of reaction started (dd/mm/yyyy)

6. Date of recovery (dd/mm/yyyy)

7. Describe reaction or problem

13. Relevant medical/ medication history (e.g. allergies, race, pregnancy, smoking, alcohol use, hepatic/renal dysfunction, etc.)

14. Seriousness of the reaction: No ☐ if Yes ☐ (please tick anyone)

☐ Death (dd/mm/yyyy) ☐ Congenital-anomaly
☐ Life threatening ☐ Required intervention to prevent permanent impairment/damage
☐ Hospitalization/Prolonged
☐ Disability ☐ Other (specify)

15. Outcomes

☐ Recovered ☐ Recovering ☐ Not recovered
☐ Fatal ☐ Recovered with sequelae ☐ Unknown

C. SUSPECTED MEDICATION(S)

S.No.	8. Name (Brand/Generic)	Manufacturer (if known)	Batch No. / Lot No.	Exp. Date (if known)	Dose used	Route used	Frequency (OD, BD etc.)	Therapy dates		Indication	Causality Assessment
								Date started	Date stopped		
i											
ii											
iii											
iv											

S.No. as per C	9. Action Taken (please tick)						10. Reaction reappeared after reintroduction (please tick)			
	Drug withdrawn	Dose increased	Dose reduced	Dose not changed	Not applicable	Un-known	Yes	No	Effect unknown	Dose (if reintroduced)
i										
ii										
iii										
iv										

11. Concomitant medical product including self-medication and herbal remedies with therapy dates (Exclude those used to treat reaction)

S.No.	Name (Brand/Generic)	Dose used	Route used	Frequency (OD, BD, etc.)	Therapy dates		Indication
					Date started	Date stopped	
i							
ii							
iii							

Additional Information:

D. REPORTER DETAILS

16. Name and Professional Address:_____

_____

Pin:_____E-mail:_____

Tel. No. (with STD code)_____

Occupation:_____Signature:_____

17. Date of this report (dd/mm/yyyy):

Confidentiality: The patient's identity is held in strict confidence and protected to the fullest extent. Programme staff is not expected to and will not disclose the reporter's identity in response to a request from the public. Submission of a report does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the reaction.

National Coordination Centre
Pharmacovigilance Programme of India
Ministry of Health & Family Welfare,
Government of India
Sector-23, Raj Nagar, Ghaziabad-201002
Tel.: 0120-2783400, 2783401, 2783392
Fax: 0120-2783311
www.ipc.nic.in

Pharmacovigilance Programme of India for Assuring Drug Safety

ADVICE ABOUT REPORTING

A. What to report

- Report serious adverse drug reactions. A reaction is serious when the patient outcome is:
  - Death
  - Life-threatening
  - Hospitalization (initial or prolonged)
  - Disability (significant, persistent or permanent)
  - Congenital anomaly
  - Required intervention to prevent permanent impairment or damage
- Report non-serious, known or unknown, frequent or rare adverse drug reactions due to Medicines, Vaccines and Herbal products.

B. Who can report

- All healthcare professionals (Clinicians, Dentists, Pharmacists and Nurses) can report adverse drug reactions

C. Where to report

- Duly filled Suspected Adverse Drug Reaction Reporting Form can be sent to the nearest Adverse Drug Reaction Monitoring Centre (AMC) or directly to the National Coordination Centre (NCC).
- Call on Helpline (Toll Free) 1800 180 3024 to report ADRs.
- Or can directly mail this filled form to pvpi@ipcindia.net or pvpi.ipcindia@gmail.com
- A list of nationwide AMCs is available at:

  http://www.ipc.gov.in, http://www.ipc.gov.in/PvPI/pv_home.html

D. What happens to the submitted information

- Information provided in this form is handled in strict confidence. The causality assessment is carried out at AMCs by using WHO-UMC scale. The analyzed forms are forwarded to the NCC through ADR database. Finally the data is analyzed and forwarded to the Global Pharmacovigilance Database managed by WHO Uppsala Monitoring Centre in Sweden.
- The reports are periodically reviewed by the NCC-PvPI. The information generated on the basis of these reports helps in continuous assessment of the benefit-risk ratio of medicines.
- The information is submitted to the Steering committee of PvPI constituted by the Ministry of Health & Family Welfare. The Committee is entrusted with the responsibility to review the data and suggest any interventions that may be required.

E. Mandatory field for suspected ADR reporting form

- Patient initials, age at onset of reaction, reaction term(s), date of onset of reaction, suspected medication(s) and reporter information.

For ADRs Reporting Call on PvPI Helpline (Toll Free)

1800 180 3024

(9:00 AM to 5:30 PM, Working Days)

Appendix 4

Useful Resources on Adverse Drug Reactions and Drug Interactions

BOOKS

1. Litt JZ, Sheer NH: Litt's Drug Eruptions and Reactions Manual (D.E.R.M.). Ohio: CRC Press, 2017.
2. Wolverton SE: Comprehensive Dermatologic Drug Therapy. Edinburgh: Elseviers Sauders; 2012.
3. Hall CJ, Hall BJ: Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy. London: Springer-Verlag, 2015.
4. French LE: Adverse Cutaneous Drug Eruptions. Basel:Karger, 2012.
5. Talbot J, Aronson JK: Stephen's Detection and Evaluation of Adverse Drug Reactions: Principles and Practice. Oxford:Wiley-Blackwell, 2011.

WEBSITES

1. Litt's Drug Eruptions and Reactions database:

   http://www.drugeruptiondata.com
2. Cochrane Skin Group:

   http://www.csg.cochrane.org
3. Cochrane Library:

   http://www.thecochranelibrary.org
4. The National Institute for Health and Clinical Excellence (NICE):

   http://www.nice.org.uk
5. Meyler's Side Effects of Drugs: The international encyclopedia of drug reactions and interactions. Aronson JK. Elsevier Science, 2015:

   http://www.elsevier.com
6. Reactions Weekly and Reaction Database-Adis Press:

   http://www.ovid.com
7. Canada's Adverse Drug Reaction Database:

   http://www.cbc.ca/news/adr/database/
8. Australian Adverse Drug Reaction Bulletin:

   http://www.tga.gov.au/adr/aadrb.htm

   http://www.medscape.com/druginfo/druginterchecker?cid=med

   http://www.drugdigest.org/DD/Interaction/ChooseDrugs
9. Med Watch:

   http://www.fda.gov/medwatch/
10. British National formulary:

    https://www.bnf.org/
11. The Merck manual:

    https://www.merckmanuals.com/professional
12. WHO Programme for International Drug Monitoring:

    http://www.who-umc.org
13. Clinical trials process for drugs:

    http:// www.bma.org.uk/ap.nsf/Content/Hubclinicaltrials
14. Free drug information service to consumers:

    http://www.drugs.com
15. Drug information database for clinicians and patient:

    http://www.medscape.com/druginfo/
16. WHO's updated and current information on essential medicines and health products:

    http://www.who.int/druginformation/
17. Information on manufacture, sale and distribution of drugs and monitoring of adverse drug reporting activity in India:

    http://www.cdsco.nic.in/
18. Maharashtra State Pharmacy Council's Drug Information Centre:

    http://www.mspcindia.org/dic

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IADVL's Textbook on

CUTANEOUS ADVERSE DRUG REACTIONS

A Comprehensive Guide

About the Book

Adverse drug reactions (ADRs) are often encountered in clinical practice, not only by dermatologists but by other medical practitioners too. Clinicians therefore need to be aware of cutaneous manifestations of ADRs in its various morphologic forms. This subject is rarely dealt with in curricula and there are not many reference books, on this niche area of interest, especially in the Indian Subcontinent. The authors and the editorial team have made a sincere attempt to fill this gap. The book aims to sensitize and guide the clinicians on the practical aspects of recognition and management of ADRs in real life situations. ADR recognition, drug withdrawal, management and reporting have been dealt systematically by experts in the field. This book aims to cater to postgraduates, practitioners and academicians alike and serve as a comprehensive guide to diagnose and manage cutaneous ADRs.

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- An updated and comprehensive account on Cutaneous Adverse Drug Reactions
- Has 52 chapters written by 85 eminent international and national authors
- Simplified format of chapters with plenty of high quality clinical images, tables, and illustrations for easy readability and comprehension
- Contains useful resources like scoring systems, drug recording proforma, patient information and counselling leaflets

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