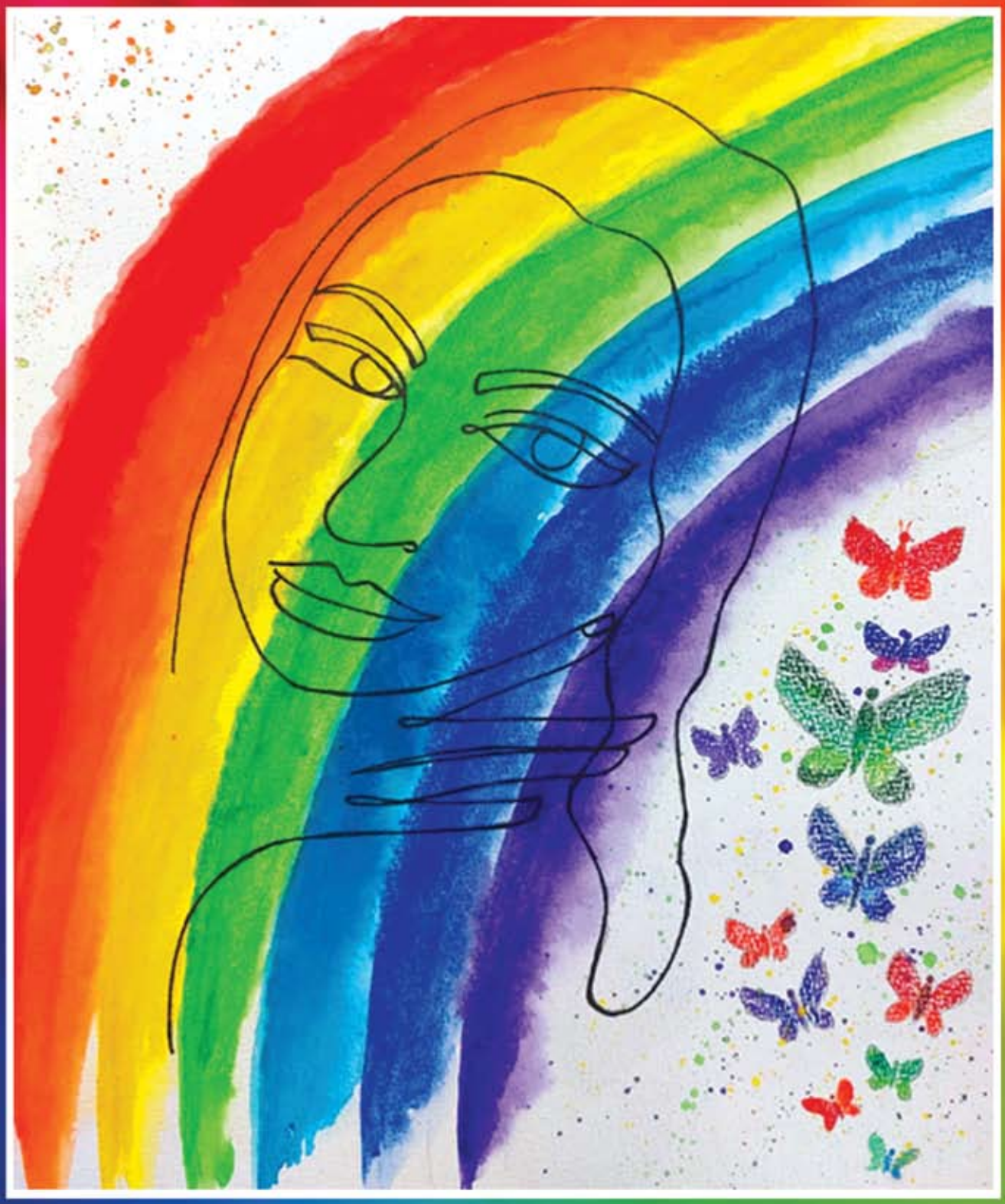
IADVL NEWSLETTER

SIG PIGMENTARY DISEASES



Designed by : Dr Swanam Gangopadhyaya

Colours of rainbow represent the myriad of conditions we have included in newsletter as well as hope for patients, female outline represents all the female brigade of our SIG and butterflies represent the beauty of life even after skin ailment.

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Dr. Surabhi Dayal
Member

Message from SIG- Pigmentary Diseases

Dr. Pooja Arora Mrig
Coordinator
Professor, Dermatology,
Dr RML Hospital & ABVIMS,
New Delhi

Dr. Pragya Nair
Convener
Professor, Dermatology,
Pramukhswami Medical
College, Gujarat

Dear Readers,

It gives me immense pleasure to bring to you this newsletter from the SIG-Pigmentary diseases. As a special interest group of the IADVL, we strive for the advancement of knowledge in the realm of pigmentary diseases and this newsletter is a step towards this endeavor.

As we are all aware, pigmentary disorders comprise a significant proportion of our practice, be it institutional or private. While hypopigmentary and hyperpigmentary disorders are the major fraction, there is a category of patients who present with non-melanin pigmentation, a topic which is not discussed much. These disorders are not so rare and can cause diagnostic confusion.

This newsletter is the product of hard work of our team that comprises of enthusiastic women dermatologists who have put their experience into words. In this, we have discussed various “shades” of non-melanin pigmentation like xanthoderma, blue skin, vascular causes, pigmentation due to heavy metals and reactions to tattoos. There is also an interesting crossword & a case vignette. We hope you enjoy reading it.

As they say, “Anyone who keeps learning, stays young.” Wishing our readers an enlightening journey of learning.

We would love to know your suggestions at drpoojamrig@gmail.com

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Hypopigmentation sans melanin: exploring the vascular causes

Dr. Guneet Awal
Associate Professor,
Department of Dermatology,
Venereology and Leprology,
S.G.R.D Institute of Medical Sciences & Research
Director & Senior Consultant Dermatologist, Skin,
Cosmetology & Laser clinic,
Amritsar Hospital, Amritsar,
Punjab

The prevalence of pigmentary disorders varies among distinct geographical regions of the world, age groups and races. Around 10.8% of patients attending dermatology OPD at a hospital were reported to have pigmentary disorders in a study conducted in adult population in Western India.[1] Pigmentary abnormalities have a significant emotional impact while frequently being considered to be simply of "cosmetic" importance. While the most common cause of hypopigmentary disorders pertains to melanin, there are few conditions with a vascular etiology. The incidence of vascular disorders manifesting as hypopigmentation is difficult to estimate since cases are usually mild and often under diagnosed. Few important vascular disorders which manifest as hypopigmentation are discussed below.

NEVUS ANEMICUS

Nevus anemicus (NA), first described by Hans Vörner in 1906, is an uncommon, congenital, nonprogressive lesion. It manifests as a solitary or multiple hypopigmented macules, characterized by ill-defined, irregularly shaped, confluent lesions that blend into the normal skin. The lesions may already exist at birth or develop later. They frequently develop on the trunk, though there are reports of lesions on face and extremities. Prevalence of NA has been estimated to be 1% to 2%, with a slight female preponderance. This might be underestimated figures due to its subtle clinical presentation, especially in lighter skin types.

Etiopathogenesis

The underlying mechanism for apparent hypopigmentation is an aberrant, increased response of the alpha-2 receptors of the lesional vasculature to catecholamines, such as epinephrine and norepinephrine. This hypersensitivity results

in permanent vasoconstriction leading to hypopigmentation of the skin. Hence, it has been called a "pharmacological naevus", which characteristically does not become erythematous in response to trauma, heat, or cold. Vigorously rubbing the lesion and surrounding skin or by applying ice or heat, will accentuate the lesion due to reactive erythema in the surrounding skin while the lesional skin remains pale. The pathogenesis of NA has been supported by various pharmacologic studies that demonstrated restoration of normal skin color after intralesional sympathetic blockade. It may be associated with port wine stains, telangiectatic nevi (nevus vascularis mixutus), Becker's nevus and some genodermatoses including neurofibromatosis and phakomatosis pigmentovascularis (PPV).[2]

Differential diagnosis

NA has to be differentiated clinically from other hypopigmented lesions including nevus depigmentosus (NDP), ash-leaf macules, hypomelanosis of Ito, vitiligo, pityriasis alba and leprosy. Woods lamp examination does not accentuate the hypopigmentation of NA, as opposed to vitiligo and NDP. Diagnosis is made by diascopy of the lesion in which pressure is exerted until the nevus blends into the surrounding pale skin. Firm stroking through lesional and non-lesional skin will elicit the triple response of Lewis in normal skin with an abrupt lack of response in nevus anemicus. Only the wheal without a flare may be visible within the confines of the lesion. Dermoscopy reveals a lack of blood vessels in the lesion's centre with a compensatory flare in the surrounding skin and blending with the surrounding.[3] On histological examination, a normal presence of melanocytes (number and distribution) and melanin is seen. Although biopsy is not diagnostic, it may be beneficial in ruling out other hypopigmentary disorders. NDP is a close differential. It is a rare cutaneous lesion that most commonly presents at birth as a hypopigmented patch, similar to NA. However, erythema is observed in the hypopigmented area after mechanical stimulation (rubbing) in case of NDP.

Management

Reassurance and counselling are of utmost importance. Patients might benefit from the application of camouflaging makeup for cosmetic purposes. Clinicians should be aware of associated abnormalities such as neurofibromatosis or vascular anomalies, as nevus anemicus might sometimes accompany these rare genodermatoses.

BIER'S SPOTS (PSEUDOLEUKODERMA ANGIOSPASTICUM)

Bier spots are characterized by multiple, asymptomatic, small, hypopigmented macules, mainly on the extensor surfaces of extremities in young adults, although they are sometimes generalised.[4] They disappear after raising the affected extremity or when pressure is applied to the surrounding skin. The intervening skin may seem erythematous but blanches with pressure so that the pale macules disappear. It is a benign physiological vascular anomaly that occur due to differential cutaneous vascular dilatation/ constriction patterns, more visible on arms than trunk. It arises from either response of cutaneous

vessels to venous hypertension or from small vessel vasoconstriction inducing tissue hypoxia. There are reports of Bier spots preceding systemic diseases, such as scleroderma renal crisis, mixed cryoglobulinaemia or lymphoma. They are less commonly seen in darker skin. The differential diagnosis includes vitiligo, post inflammatory hypopigmentation, tinea versicolour and other hypopigmented macules. Dermoscopic findings show pale white macules with white structureless areas lacking vessels. These dermoscopic findings may disappear when the arms are raised.[5]

Bier spots are often idiopathic and regress spontaneously, hence no treatment is required.

WORONOFF RING

A ring-like zone of hypopigmentation surrounding resolving psoriasis lesions is known as Woronoff ring. Its occurrence has been a conundrum, inspite of it being first described more than 100 years ago, by Dr D. L. Woronoff, a dermatologist at Moscow University in Russia. Although early accounts of pathogenesis of Wornoff ring talked about disturbed vascularization and disturbed prostaglandin metabolism. However, the plausible explanation of its origin is now linked to the recent advances in the understanding of pathogenesis of psoriasis. The production of interleukin-17, interleukin-22 and tumour necrosis factor-α by pathogenic CD8+ T cells in Psoriasis lead to synergistic action on melanocytes, thereby, increasing their proliferation while inhibiting melanogenesis. As a consequence, there is development of a hypopigmented zone at the edge of regressing psoriastic plaques, which becomes evident as the Woronoff ring.[6]

The width of wornoff ring is usually between 2 and 6 mm, with regional variations. Size increases with the size of the central psoriatic plaque. Although there can be a spontaneous occurrence, Woronoff ring has been reported after ultraviolet (UV) phototherapy or photochemotherapy, topical treatment, such as anthralin or glucocorticosteroids, or systemic treatments including fumaric acid esters or the tumour necrosis factor (TNF)-α antagonist adalimumab.

OTHER MISCELLANEOUS CAUSES

The pallor of skin is seen in all types of anemia. The Integrated Management of Childhood Illness (IMCI) program of WHO recommends the use of simple clinical sign like palmar pallor to diagnose anemia, which is useful in high prevalence settings like India. In anemia, lack of oxyhaemoglobin accounts for the pale appearance of skin, thus appearing lighter in color. Also, according to a recent study, in most of the patients with Fanconi Anaemia, there was at least 1 cutaneous pigmentary change, with the majority developing before adolescence. Both hypopigmented and hyperpigmented pigment macules were observed including faint and ill-defined café-au-lait macules, hypopigmented skin-fold freckle-like macules and the concurrence of hypopigmented and hyperpigmented macules.[7]

Raynaud's phenomenon is usually a manifestation of underlying systemic disease. The underlying mechanism of Raynaud's phenomenon (Fig 1) is episodic vascular constriction.

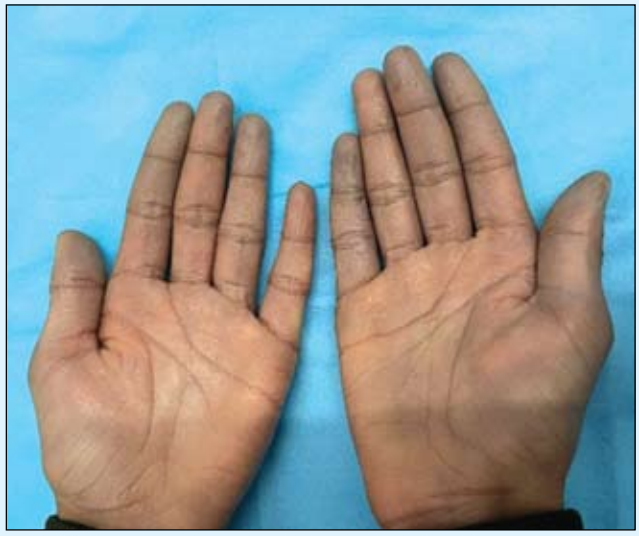


Fig 1 Raynaud's phenomenon in a patient.

Work up did not show any underlying cause

CONCLUSION

Hypomelanoses encompasses a wide array of pigment and non-pigment disorders. It is imperative to focus on the practical aspects and differential diagnosis of these conditions. Clinical acumen along with dermoscopy and histopathology in certain cases leads to clinching the diagnosis of these disorders of vascular hypopigmentation. Additional research on various pathogenetic mechanisms of these vascular hypopigmentations would be critical in determining associated conditions.

REFERENCES

1. Sayal SK, Das AL, Gupta CM. Pattern of skin diseases among civil population and armed forces personnel at Pune. Indian J Dermatol Venereol Leprol. 1997; 63:29–32
2. Ruggieri M, Milone P, Pavone P, Falsaperla R, Polizzi A, Caltabiano R, et al. Nevus vascularis mixtus (cutaneous vascular twin nevi) associated with intracranial vascular malformation of the Dyke-Davidoff-Masson type in two patients. Am J Med Genet A. 2012; 158:2870-80.
3. Thakur V, Dev A, Vinay K. Dermatoscopy of nevus anemicus. Indian Dermatol Online J 2022; 13:822-3.
4. Fan YM, Yang YP, Li W, Li SF. Bier spots: six case reports. J Am Acad Dermatol. 2009 ;61:e11-2.
5. Sasaki K, Iinuma S, Tsuruta N, Kanno K, Kishibe M, Honma M, et al. Dermoscopy of Bier spots. Eur J Dermatol. 2020;30:300-301.
6. Prinz JC. The Woronoff Ring in Psoriasis and the Mechanisms of Postinflammatory Hypopigmentation. Acta Derm Venereol. 2020;100:adv00031.
7. Ruggiero JL, Dodds M, Freese R, Polcari IC, Maguiness S, Hook KP et al. Cutaneous findings in Fanconi anemia. Journal of the American Academy of Dermatology. 2021;85:1253

Xanthoderma (Yellow skin): Causes and approach

Dr. Chethana S G
Assistant Professor,
JSS medical college, Mysuru

Xanthoderma is a term derived from Greek, meaning ''yellow skin'' and describes any yellow to yellow-orange macular discoloration of the skin. The colors reflected from the skin are important indicators of dermatologic and systemic disorders. Incident light is subject to absorption by chromophores in the skin and scattering. Chromophores associated with yellow light reflection include the carotenoids and bilirubin. Yellow skin disorders are a heterogenous group composed of abnormalities in keratin, elastic and connective tissue, lipid metabolism and other states of metabolic, inflammatory, or organ dysfunction. Dermatologists have an essential role in identifying these conditions. Especially the ones with malignant or systemic associations, to ensure early diagnosis and treatment.

The three qualities of visible light include chroma (purity), value (lightness or darkness), and hue (color)1. Hue is the most obvious visible characteristic of use in clinical assessments. Yellow is the color the human eye sees when it receives light with a dominant wavelength between 570-590nm. A yellow hue may develop through a range of pathophysiologic mechanisms which will be explored in this review to help clinicians answer the question.

Chromophore is the word used to describe the moiety within the pigment molecule responsible for its color. There are both endogenous and exogenous yellow chromophores that color the skin. Endogenous yellow chromophores include the hemoglobin breakdown products bilirubin, biliverdin, and urobilin. Urobilin, also known as urochrome, is the molecule responsible for the yellow color of urine. Exogenous chromophores include those directly applied or inserted into the skin, such as cadmium sulphide in tattoos and those obtained through dietary ingestion including the carotenoids. In normal human physiology, adipose tissue, plasma, and skin have a yellow hue (excluding the skin of Fitzpatrick skin types IV-VI).

Table 1- Various causes of yellow skin

Group	Disorders
Inherited disorders	Palmoplantar keratodermas, familial hyperlipidemia-related xanthomatoses, pseudoxanthoma elasticum (PXE), and some disorders with a genetic predisposition to tumors.
Acquired disorders:	**Exogenous:** Carotenoderma, cumulative sun exposure, iatrogenic intervention with medications, nutritional intake, or direct contact of substances with the skin, such as topical ascorbic acid application, tobacco smoking, or sunless tanning products **Endogenous:** Disorders associated with biliary or hepatic disease, renal failure, endocrine disorders, inflammatory and auto-immune disease, depositional disorders, and malignancy amongst others[1]

Jaundice, also known as icterus, is a yellow discoloration of epithelia caused by bilirubin deposition in elastic tissues. The conjunctivae, episclerae, and sublingual tissues are rich in elastic fibers and are usually affected before the skin. Jaundice is always accompanied by hyperbilirubinemia, and usually occurs at a serum total bilirubin of approximately 3.0 mg/dL. The numerous causes of hyperbilirubinemia, include infectious, autoimmune, neoplastic, genetic, toxic, and drug-related conditions. Jaundice develops through pre-hepatic, intrahepatic, and post-hepatic mechanisms.

Hypercarotenemia may be genetic (familial carotenemia) with normal dietary intake but failure in metabolism of vitamin A, or due to systemic disease, or excessive carotenoid ingestion from eating large quantities of green, yellow, and orange vegetables. Thyroxine accelerates the conversion of beta-carotene into two molecules of retinol (vitamin A). This presents with a yellow hue predominant on the acral surfaces and the nasolabial folds, sparing the sclera and mucous membranes. Carotenes are excreted by the colon and epidermis, with accumulation in the stratum corneum in states of excess. It may persist clinically for up to 5 months after normalization of dietary intake when due to diet.

Lycopene is excreted by sebaceous and eccrine glands and partly reabsorbed by the horny layer of the skin.

Topical application of the fake tanning product **dihydroxyacetone (DHA)** reacts with lipids in the epidermis to form melanoidin, creating a yellow-brown color which is more pronounced on palms due to skin thickness and basal layer penetration.

Hyperkeratosis is also found on friction prone areas as a side-effect of sorafenib or sunitinib multikinase inhibitors. Yellow chromonychia may be due to thickening or dystrophy of the nail plate as found in onychomycosis, yellow-nail syndrome, lichen planus, or due to jaundice, smoking, or topical product application

(e.g. ascorbic acid)[3]. Yellowing of the lunulae can be caused by exposures to insecticides and weed killers (dinitroorthocresol, diquat, and paraquat), and tetracycline. Nail plate yellowing is associated with smoking (nicotine sign), and the term ''harlequin nail'' is a marker for abrupt smoking cessation. In psoriasis, localized areas of yellowing of the nail as a result of subungual parakeratosis, termed ''oil spots.'' The yellow nail syndrome is thickening and a yellow to yellow-green discoloration of the nail plate associated with systemic disease. Yellowing of the hair can be caused by excessive cigarette use because of airborne smoke. It can also occur with the topical use of anthralin, used on the scalp for both psoriasis and alopecia areata.

Palmar crease xanthomas are yellow plaques in the palmar creases associated with familial dysbetalipoproteinemia. Diffuse plane xanthomas are yellow plaques that can be widely distributed. Normolipemic diffuse plane xanthomatosis may be associated with a lymphoproliferative disorder or biliary cirrhosis.

Lichen aureus is a type of pigmented, purpuric eruption in which focal lichenoid inflammation leads to extravasation of red blood cells in the dermis. The red cells are broken down in the skin to create a yellow-gold color. Sebaceous nevus is a congenital disorder presenting in infants as a yellow plaque on the head and neck, especially the scalp. Depositional disorders, such as gout due to hyperuricemia or calcinosis cutis, present with yellow/cream colored papules and nodules usually on the extremities.

Cutaneous Langerhans and non-Langerhans cell histiocytoses are diverse, encompassing such disorders as juvenile xanthogranuloma, xanthoma disseminatum and necrobiotic xanthogranuloma.

Cutaneous mastocytoma which may appear clinically as a red nodule. Dermatoscopy shows light brown blot , pigment network and yellow orange blot. Lipids present in sufficient volume will also be visible dermatoscopically as a yellow color4. Non-polarized light is better for observing superficial skin layers, yellow color (keratin).

If the diagnosis is not obvious clinically, histologic assessment of yellow skin disorders is performed using standard staining techniques, and supplementary tests including stains for lipids (e.g. Oil-Red-O), immunohistochemistry, and immunophenotyping when indicated. The common histologic findings associated with a yellow color include:

a. Hyperkeratosis
b. Intracellular or dermal deposition of lipids
c. Sebaceous and elastic tissue disorders.

Table 2: Differential diagnosis of yellow skin based on the type of skin lesion[5]	
Morphology	**Differential Diagnosis**
Macular/ Patches	**Xanthodermatoses:** Palmar crease xanthoma, Diffuse plane xanthomatosis **Infectious:** Slough **Inflammatory:** Lichen aureus **Photo-induced:** Solar elastosis **Traumatic:** Ecchymoses
Plaques/Crusted	**Infectious:** Impetigo, Onychomycosis, Trichomycosis axillaris and pubis **Keratin related:** Palmoplantar keratodermas, Hystrix epidermolytic hyperkeratosis, Ichthyosis Hystrix, Keratoderma blenorrhagicum, Actinic Keratosis, Viral Keratosis, Sorafenib/Sunitinib induced hyperkeratosis, Yellow nail syndrome, Seborrhoeic keratosis, Pachyonychia congenita. Dystrophic nail disorders (lichen planus). **Congenital:** Connective tissue nevus. **Metabolic:** Xanthelasma, Plane Xanthoma , Diffuse plane xanthomatosis. Primary hyperlipoproteinemia, Secondary hyperlipoproteinemia (DM, Obstructive liver disease, DM, Cerebrotendinous Xanthomatosis, Phytosterolemia, Pancreatitis, Estrogen). **Immunologic:** Verruciform xanthoma, Necrobiosis lipoidica diabeticorum
Papular/ Nodular	**Histiocytic:** LCH, Benign Cephalic Histiocytosis, Juvenile Xanthogranuloma, Erdheim-Chester disease, Progressive nodular histiocytosis, Xanthoma disseminatum, Xanthomatous Dermatofibroma, Retichulohistiocytosis (Solitary or Multiple) **Sebaceous:** Sebaceoma, Sebaceous adenoma, Sebaceous carcinoma, Sebaceous Gland Hyperplasia, Nevus Sebaceous, Nevus Sebaceous Syndrome, Fordyce spots **Adipose:** Piezogenic pedal papules, Fat herniation, Nevus lipomatosus superficialis, Goltz syndrome **Photo-induced:** Colloid milium, Papillary Dermal Elastolysis (PDE), Favre-Racouchot syndrome. Keratoelastoidosis marginalis **Cystic:** Steatocystoma multiplex, Epidermal cyst, Pilomatricoma **Elastic:** PXE, Buschke-Ollendorf Syndrome, Mid-dermal elastolysis (type-II), Elastomas, Elastosis perforans serpiginosum **Metabolic:** Tendon Xanthoma, Tuberous Xanthoma, Tuberoeruptive Xanthoma, Eruptive xanthomata, Gouty tophi, Calcinosis cutis, Lipoid Proteinosis **Immunological:** Cutaneous mastocytoma, Necrobiotic Xanthogranuloma **Tumoral:** Keratoacanthoma, Squamous Cell Carcinoma

Vesicular/ Bullous	**Autoimmune:** Bullous Pemphigoid, Bullous Lupus Erythematosus, Linear IgA disease, Pemphigoid Gestationis. EBA **Infectious:** Bullous impetigo, Eczema herpeticum, Crusted Herpes Simplex, Varicella Zoster Virus (Shingles) I**atrogenic:** Fixed Drug Eruption
Pustular	**Generalised:** Acute Generalised Exanthematous Pustulosis (AGEP), Subcorneal Pustular Dermatosis, Pustular Psoriasis, Folliculitis, Erythema Toxicum Neonatorum, Transient Neonatal Pustular Melanosis, Ofuji disease. **Localised:** Folliculitis, Comedonal Acne, Acneiform drug eruption, Acrodermatitis Continua, Rosacea, Perioral Dermatitis, Palmoplantar Pustulosis, Eosinophilic Folliculitis, Cutaneous candidiasis, Erosive pustular dermatosis of the scalp.
Generalised/ Regional	**Iatrogenic:** Quinacrine (Mepacrine) **Behavioural:** Nicotine staining, Fake-tan (DHA), Cadmium Tattoo, Henna, Anorexia Nervosa, Turmeric **Dietary:** Carotenemia (Familial carotenemia), Lycopenemia **Organ dysfunction:** Jaundice (hepatic, hemolytic), Renal failure, Hypothyroidism, Diabetes Mellitus, Biliary disease

Conclusion

A thorough history and focused physical examination should be able to help narrow the evaluation and treatment options for these patients. Indeed, xanthoderma can be a clue to underlying life-threatening disease.

References

1. Elliot AJ. Color and psychological functioning: a review of theoretical and empirical work. Front Psychol. 2015;6:368.
2. Justin M. Haught, Shaily Patel, Joseph C. English, III,. Xanthoderma: A clinical review. J Am Acad Dermatol 2007;57:1051-8.
3. Dong H, Wang Y. A case of yellow chromonychia and yellow skin induced by topical ascorbic acid. Australas J Dermatol. 2019;60:145-147.
4. Banuls J, Arribas P, et al. Yellow and orange in cutaneous lesions: clinical and dermoscopic data. J Eur Acad Dermatol Venereol. 2015;29:2317-25.
5. I.T. Logan and R.A. Logan, The color of skin: Yellow diseases of the skin, nails, and mucosa, Clin Dermatol. 2019;37:580-90.

Pigmentary disorders due to heavy metals

Dr. Hima Gopinath
Associate Professor, AIIMS, Mangalagiri

Metals are integral to human health and have played an important role in society since the Bronze Age. However, many metals are toxic, and some lead to pigmentary disorders. A metal's density or atomic weight does not correlate well with its toxicity; thus, the term 'heavy metal' is not preferred. Important pigmentary disorders caused by exogenous metals are discussed below:

1. Argyria : Argyria, or silver-induced cutaneous pigmentation, is derived from the Greek word 'argyria' which means silver. It may be generalized or localized. In the past, colloidal silver was ingested for medicinal purposes.

Generalized argyria has also been reported after consumption of silver-containing dietary supplements, homeopathic medication, and silver-coated betel or cardamom. It presents with diffuse blue-grey pigmentation. The pigmentation is more pronounced in sun-exposed areas, sparing the creases. Light-induced reduction of silver occurs in sun-exposed areas. Argyria can affect nails ('azure lunula'), oral mucosa, cornea, and conjunctiva

Differential diagnoses include drug-induced pigmentation, other metal (such as mercury, bismuth, gold, and arsenic) induced pigmentation, and systemic conditions such as hemochromatosis, Wilsons disease, ochronosis, methemoglobinemia, and cyanosis. Localized cutaneous argyria is seen after percutaneous absorption of silver through sweat pores or wounds or traumatic implantation. Localized cutaneous argyria has been reported with occupational exposure, silver application on wounds, silver filigree in hernia repairs, silver acupuncture needles, and ear or nose piercing with silver. Amalgam silver tattoo has been reported in the oral mucosa. It present with blue-grey pigmented macules and papules.. Use of topical silver nitrate may also lead to grey-black staining of fingernails. The differential include blue naevi, metastatic melanoma, dysplastic naevi, traumatic tattoos, angiomas, and genital lentiginous or melanosis.

Dermoscopy reveals homogenous blue to brown-black, blue-black, or blue-grey coloured macules without structures and blurred borders in localized argyria. It mainly affects ridges in the palms. Tiny grey dots are seen in generalized argyria. On reflectance confocal microscopy and high-definition optical coherence tomography, small hyper-reflective particles are seen arranged in clusters or forming a network in the papillary dermis. In skin biopsy, small multiple brown-black particles are seen on the basement membrane of sweat glands, elastic fibres of the papillary dermis, the connective tissue around the pilosebaceous gland, arrector pili, and perivascular and perineural location. There is an increase in melanin. A large ellipsoid granule may be seen in degenerated connective tissue. Ochre-coloured collagen and elastic fibres ('pseudo-ochronosis') have been reported in localized argyria. There is an increase in melanin. Darkfield microscopy reveals refractile particles in a dark background ('stars in heaven appearance'). In transmission electron microscopy, electron-dense bodies are seen. The bodies are larger in exposed skin on scanning electron microscopy. Energy-dispersive X-ray spectroscopy may be used to confirm the diagnosis.

Treatment- Sunprotection may be useful. Q-switched Nd-Yag laser and 755 alexandrite lasers have been reported to be useful.

Chrysiasis

Chrysiasis is the permanent discoloration of the skin after prolonged exposure to parenteral gold. It has its origins in the Greek word 'chrysos' from 'chrysanthos' or 'golden flower'. Gold was used in the past for conditions such as rheumatoid arthritis, tuberculosis, psoriasis, and systemic lupus erythematosus. Medicinal gold compounds used include sodium aurothiomalate, disodium aurothiomalate, sodium aurothioglucose, sodium aurothiosulfate, and auranofin.

Chrysiasis starts with a mauve discolouration in the periorbital area which turns into greyish-blue or purplish-blue colour. The pigmentation is photo distributed, mainly affecting the face and sparing the creases. Covered areas become pigmented after exposure to ultraviolet light. The pigmentation begins after a few months or years of use. The severity is dose-dependent and begins at around 19 mg/kg of exposure to elemental gold. Deposition may also occur in the oral mucosa, cornea, conjunctiva, and lens. Localized cutaneous chrysiasis has been reported after implantation of gold-plated acupuncture needles, laser treatment in a patient who had received parenteral gold, lightning-induced implantation of gold from a necklace, and gold microparticle (GMP) based laser for selective photothermolysis in acne vulgaris. Lichenoid dermatitis has been reported after consuming gold-containing alcoholic beverage.

Non-specific homogenous blue-grey pigmentation was reported on dermoscopy in a case of localized chrysalis. Reflectance confocal microscopy revealed hyperreflective subcellular pinpoint particles. In skin biopsy of generalized chrysiasis, there are small, irregular oval, or round black granules in macrophages of the dermis, predominantly in the perivascular location. They may also be seen in fibroblast-like cells. The granules are larger than silver granules and can be seen well in darkfield microscopy. An increase in melanin has been reported both in the dermis and epidermis. 'Orange-red birefringence' is seen

on polarised microscopy. Electron microscopy reveals 'aurosomes', electron-dense particles in the phagolysosomes of macrophages. Gold can be measured with graphite furnace atomic absorption spectrometry and inductively coupled plasma mass spectrometry. Tissue gold can be diagnosed with methods such as proton-induced X-ray emission and neutron activation analysis.

Treatment- Sun-avoidance. Q-switched laser has contraindicated a sit can lead to permanent worsening. Improvement has been reported with a pulsed dye laser.

3. Arsenicosis

Arsenic is a metalloid found in both soil and water. Chronic arsenic poisoning can occur through environmental, occupational, or medicinal exposure.

Skin manifestations occur after 2-9 years of exposure. There can be spotted pigmentation, diffuse pigmentation with scattered pale macules ('rain drops on dusty road'), leukomelanosis, idiopathic guttate hypomelanosis-like lesions, and argyria-like pigmentation with hypopigmented macules. The pigmentation is more in pigmentation-prone areas such as the axilla, groin, areola, and areas with pressure or friction. The pigmentation may be due to arsenic deposits and an increase in melanin. Brownish discoloration and Mees lines may be seen on the nails. Periungal pigmentation has been reported in acute arsenic poisoning. Non-tender hyperkeratotic papules are seen on the palms and soles. The keratotic papules may be a few pinhead-sized papules or multiple larger keratotic papules. They may coalesce to form plaques, diffuse keratoses, and large verrucous growths. Keratoses can enlarge and undergo malignant transformation. Skin cancers mainly on unexposed upper extremities and trunk, simultaneous keratoses and pigmentation, multiple simultaneous skin cancers, and young age of presentation are clues to arsenicosis. Arsenic levels can be measured in skin, hair, urine, and nails.

Treatment-Stopping further exposure to arsenic is essential. Regular follow-up is important due to the long latent period for malignancies. Treatment modalities include sun protection, vitamin, mineral, anti-oxidant supplementation, oral retinoids, and surgical removal or chemotherapy for keratoses and chelating agents.

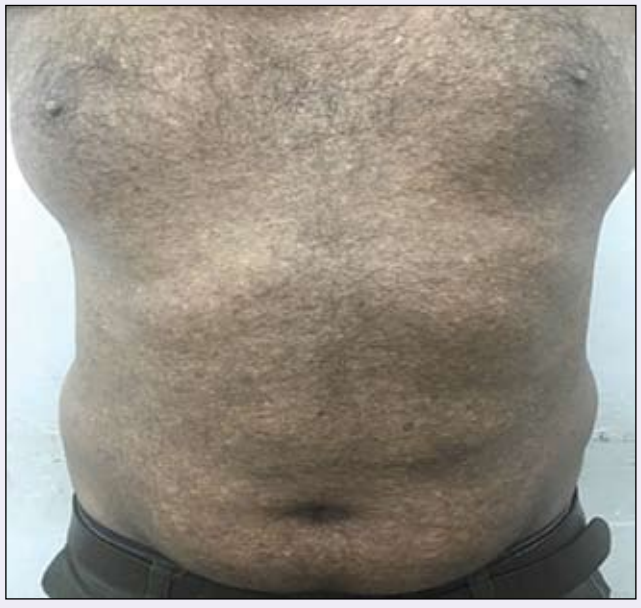


Fig 1- Mottled pigmentation due to ingestion of ayurvedic medication (containing arsenic)

Others

Mercury: Prolonged cutaneous exposure to mercury from skin-bleaching creams causes a slate-grey pigmentation. The pigmentation is more prominent in the creases. Percutaneous

absorption occurs through the appendages. Pigmentation may be due to the tattoo effect and increase in melanin. Chronic systemic exposure can lead to a pigmentation line in the gingival margin similar to lead and bismuth. Deposits may also occur in the cornea and anterior capsule of the lens ('mercurialentis'). In skin biopsy, coarse brown-black granules are seen mainly in the papillary dermis. Refractile granules are seen on dark field microscopy. Mercury pigmentation can be diagnosed with electron microscopy and neutron activation analysis. Generalized lichenoid dermatitis due to metallic mercury vapor poisoning has been reported in a family. Although mercury in amalgam is generally implicated in oral lichen planus, a case of lichen planus pigmentosus in a child was attributed to dental mercury amalgam.

Bismuth: Bismuth was used in the management of venereal diseases in the past. Generalized pigmentation resembling argyria occurs with chronic bismuth ingestion. Oral and conjunctival pigmentation may occur. Blue-black gingival line may be seen. Small metallic bismuth particles can be seen in the papillary and reticular dermis in a skin biopsy. Transient macular 'black tongue' has been reported after bismuth subsalicylate-containing antacid use.

Lead: Gingival pigmentation with a lead line ('Burtons's line') is seen in chronic lead poisoning. Lead granules, deposited in the sub-epithelium, are converted to lead sulphide.

Iron: The topical use of iron salts such as ferric subsulphate, ferric chloride, and iron sesquioxide has caused brownish discoloration of the skin. Thus, the use of iron salts should be avoided for hemostasis in facial skin, and they are contraindicated in diagnostic biopsies of pigmented lesions.

Zinc: A black irregular macule has been reported following repeated application of zinc oxide on chapped lips. A skin biopsy revealed submucosal fine golden yellow granules deposited mainly on elastic fibres.

References:

1. Weedon D. Cutaneous deposits. In: Weedon D., editor. Weedon's Skin Pathology. 3rd ed. Churchill Livingstone; Edinburgh, UK: 2010. pp. 369–396. Chapter 14.
2. Cohen PR. The color of skin: blue diseases of the skin, nails, and mucosa. Clin Dermatol. 2019;37:468-86.
3. Smith RW, Leppard B, Barnett NL, Millward-Sadler GH, McCrae F, Cawley MI. Chrysiasis revisited: a clinical and pathological study. Br J Dermatol. 1995;133:671-8.
4. Ratnaike RN. Acute and chronic arsenic toxicity. Postgrad Med J. 2003;79(933):391-6.
5. Rossy KM, Janusz CA, Schwartz RA. Cryptic exposure to arsenic. Indian J Dermatol Venereol Leprol 2005;71:230-5.
6. Granstein RD, Sober AJ. Drug- and heavy metal-induced hyperpigmentation. J Am Acad Dermatol. 1981;5:1-18.
7. Drakensjö IT, Lengstam I, Hedblad MA. Skin discoloration caused by iron salts. Acta Derm Venereol. 2014;94:92-3.

Ink's Impact: Exploring Tattoo and their reactions

Dr. Priyadarshini Sahu
Consultant Dermatologist,
Post Graduate Institute of Medical Education & Research (PGIMER), Chandigarh

Introduction: Tattoo processing is related to introduction of exogenous pigment, which give dermal colour for permanent desired pattern.[1] Tattoos can be medical and decorative. Over past few decades, the popularity of decorative tattooing has grown up exponentially, especially among adolescents and young adults. This is accompanied by increase in incidence of complications Unfortunately, there are no legislations to promote safe tattooing. The aim of this review is to summarise cutaneous complications associated with tattoo.

Complications due to tattooing can be classified as acute and chronic complications. Acute reactions occur immediately after 7 days of application of pigment into the skin, while chronic reactions occur after months or years. It has been seen in most of the studies that coloured tattoo especially red produce more adverse skin reaction as compared to black tattoo.[2,3]

Components of Tattoo ink: Till now FDA has not approved any pigments for injection into the skin for cosmetic purpose. Likewise, in Europe also there are no standard regulations. Tattoo ink consists of a carrier and pigment. Carrier works like a solvent for the pigment. Currently, metallic salts and organic dyes are used as pigments. Modern-day colorants are mainly organic, containing azo or polycyclic pigments. However, antimony, cadmium, lead, chromium, cobalt, nickel, and arsenic may still be present as contaminants.3 Dyes can be of various colours. Most commonly used colour is black, which consist of iron oxides and diverse carbons. Green inks consist of chromium and copper, yellow cadmium salts; blue ink is composed of chromium, cobalt and copper salts; and red ink includes high levels of mercury. According to latest report, black, blue and red inks have carcinogenic potential.

Various complications associated with tattoos are highlighted in Table 1

Table 1: Complications due to tattooing

Complications of Decorative tattooing	Clinical features	Onset of symptoms
Allergic reactions	• Allergic dermatitis • Immediate IgE-Mediated Tattoo Reactions • Delayed type IV hypersensitivity • Photoallergic reactions	Immediately after days to weeks After sun-exposure
Bacterial infections	Impetigo, Ecthyma, Abscess, Erysipelas, Gangrene, Sepsis, Cellulitis Lepra, Syphilis, Tetanus	Within few days After weeks to years
Viral infections	• Molluscum contagiosum • Verruca vulgaris • Hepatitis B, C • HIV	After weeks to months
Fungal infections	• Tinea • Zygomycosis	After weeks to months
Malignancy	• Lymphoma • Melanoma • BCC/SCC • Keratoacanthoma • Dermatofibrosarcoma protruberans	After years
Cutaneous conditions localised to tattoo area	• Psoriasis • Lichen planus • Morphea • Pseudolymphoma • Pyoderma gangrenosum • Cutaneous lupus erythematosus • Pseudoepitheliomatous hyperplasia	After weeks to months

Fig 1: Lichenoid reaction to red tattoo

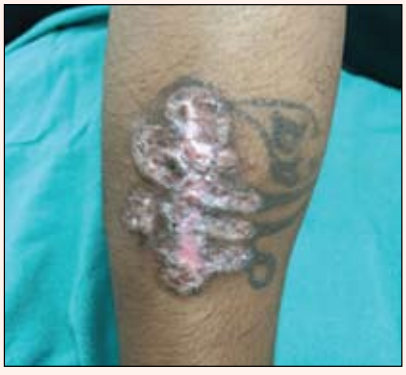


Figure 2a, b: Granulomatous reaction to red ink in tattoo. Note sparing of green color

Complications of Decorative and Accidental tattooing (Table 1):

Infections:

Tattooing can result in penetration of potentially infectious agents, including bacteria, viruses, and fungi. Routes of transmission include contaminated tattoo needles, gloves, ink, water used to dilute tattoo ink, and improper tattoo after care of the client. The most significant issue is potential for hepatitis B (HBV) and C virus (HCV) as well as HIV transmission. Under present day-improved hygiene standards, the transmission of these diseases has reduced significantly. Due to risk of transmission of these viruses, "tattooed people" may be banned from donating blood for 4 months to 1 year following tattooing to limit the potential spread of infections, depending on local laws and regulations.[4]

Bacterial infections: Nowadays, most common infections are superficial, of bacterial origin and occur within a few days after tattooing. Though, more severe systemic infections can occur such as cellulitis, erysipelas, necrotizing fasciitis, or bacterial endocarditis. The most common bacteria include Staphylococcus aureus, Streptococcus pyogenes, Clostridium difficile, and Pseudomonas aeruginosa. Signs and symptoms usually manifest between 4 and 22 days after tattooing.

Viral infections: Local viral infections like herpes simplex virus, human papilloma virus, and molluscipox virus has been reported. Usually, verrucae and MCV infection occur years after tattooing. This might be due to an alteration of the local immune system especially with UV exposure. Systemic viral infections such as HIV, hepatitis B and C can be transmitted during tattooing.

Fungal infections: Fungal infections, such as Aspergillus fumigatus and parasitic infections such as Leishmaniasis are rarely reported in tattoos.

Suppurative Granulomatous Reactions: This reaction pattern is associated with non-tuberculoid mycobacteria. The clinical presentation is characterized by erythematous pruritic papules, nodules, pustules and ulcers, abscesses, or plaques. Most common causes of this reaction is Mycobacterium chelonae. Signs and symptoms usually manifest as early as 1-month post-tattooing. If granulomatous lesions are seen, a biopsy is required with tissue culture and PCR for mycobacterium typing. Without waiting for the results, antibiotic therapy should be started, and if required in case of resistance to conventional therapies, the therapy can be altered later. Leprosy and tuberculosis have also been described after tattooing.

Thus, to prevent contamination, hygiene regulation should be followed. Despite these regulations, infections are still the most frequent tattoo complication. Bacterial infection has been seen in approximately 1–5% of tattooed individuals.

Allergic and Foreign body reactions:[1]

Dichromate (green), cadmium (yellow), cobalt (blue) and mercury salt (red) based pigment and their degradation products are responsible for reaction. Contamination of pigment with nickel and other organic ingredients such as azo dyes and quinacridone can cause marked allergic reactions. Azo dyes lead to photosensitizing reaction in

tattoo dyes when they are exposed to sunrays. The duration between the occurrence of reaction and tattooing varies from few days to several years. The clinical picture varies from contact urticaria like reaction, photoallergic reactions, eczematous, lichenoid or pseudolymphomatous lesions .

Granulomatous Reactions :

Granulomatous reaction can be tuberculoid, sarcoid or necrobiotic granulomatous reaction. Tuberculoid granuloma can be associated with leprosy, tuberculosis or mycobacterial infections. It may occur with exposure to pigments, like ferric oxide and chromium salts. Sarcoid granuloma may be present alone or may be a part of systemic sarcoidosis. Focal alterations in dermal connective tissue surrounded by histiocytes is seen with necrobiotic granuloma. It is associated with granuloma annulare and necrobiosis lipoidica.

Spongiotic dermatitis :

Spongiotic dermatitis may result from diluent, topical antiseptics/ointment, and ink, which is used along with tattooing. The affected area becomes erythematous and oedematous, occasionally develop vesicular dermatitis. In case of more chronic inflammatory dermatitis, it progresses to prurigo nodularis. Histopathology reveals epidermal spongiosis and dermal infiltrate with lymphocytes, macrophages, eosinophils, and plasma cells.

Lichenoid Reaction:

It is one of the most common types of sustained tattoo reaction. It is characterised by presence of flat-topped papules or plaques within the area of tattoo suggesting lichenoid reaction. On histology a band like infiltrate of lymphocytes at dermo-epidermal junction and vacuolar alteration of basal keratinocytes. Treatment includes topical or intralesional corticosteroids, finally require removal of affected skin.

Neoplasms:

Benign lesions like epidermal cysts, milia, histocytofibroma and seborrheic keratosis are well known after tattooing. Various neoplasms mainly squamous-cell carcinoma, keratoacanthoma, basal cell carcinoma, and melanoma have been reported after tattooing.5 Various factors such as intradermal injection of potential carcinogenic substances (benzapyrene in black tattoo ink), genetic factors and UV radiation exposure may be responsible for its occurrence. However, true association is difficult to determine.

Autoimmune dermatoses:

Autoimmune disorders such as psoriasis, lichen planus, non-segmental vitiligo, lupus erythematosus and lichen sclerosus in tattooed skin has been described.2 Koebner's phenomenon is the possible explanation. According to this, trauma of tattooing procedure can provoke inflammatory response resulting in local flare of these dermatosis. Thus, patients must be warned about flare of autoimmune disease prior to tattooing.

Chronic inflammatory black tattoo reactions (CIBTR)[4]

It is one of the common tattoo complications especially with black colour tattoo. It is clinically characterized by chronic papules or nodules, strictly limited to only the black tattooed skin, and hence also named as 'papulo-nodular' reactions. The symptoms generally include mild itch or pain. Histopathology is mainly granulomatous inflammation. These reactions are known to be a possible manifestation of sarcoidosis, tattoo-

associated uveitis, or non-sarcoidosis.

Management:

With increasing incidence of tattoo reactions, clinicians must be able to recognise and treat these reactions at the earliest. Diagnosis can be made on basis of clinical history and examination. However, in case of doubt, biopsy should be done. Allergic reactions can be managed with topical, intralesional and systemic corticosteroids. For lichenoid reactions topical tacrolimus is useful. Bacterial infections can be diagnosed with appropriate culture and managed accordingly. Appropriate antiviral and antifungal agents are required for viral and fungal infections. Tumors can be removed surgically depending on the site or size of the lesions with or without lymph node removal.

Conclusion:

There is an urgent need to increase awareness among the adolescents regarding the increase risk of complications associated with tattooing. Moreover, parlours doing tattooing should also be educated about the risks involved and importance of using proper infection control procedures. Also, with the growing popularity of tattooing in the younger generation it is time for the government to issue regulations with regard to the components of tattoo ink.

References:

1. Khunger N, Molpariya A, Khunger A. Complications of Tattoos and Tattoo Removal: Stop and Think Before you ink. J Cutan Aesthet Surg. 2015;8:30-6.
2. Wenzel SM, Rittmann I, Landthaler M, Bäumler W. Adverse reactions after tattooing: review of the literature and comparison to results of a survey. Dermatology. 2013;226:138-47.
3. Islam PS, Chang C, Selmi C, Generali E, Huntley A, Teuber SS et al. Medical Complications of Tattoos: A Comprehensive Review. Clin Rev Allergy Immunol. 2016;50:273-86.
4. van der Bent SAS, Rauwerdink D, Oyen EMM, Maijer KI, Rustemeyer T, Wolkerstorfer A. Complications of tattoos and permanent makeup: overview and analysis of 308 cases. J Cosmet Dermatol. 2021;20:3630-41.
5. Serup J, Carlsen KH, Sepehri M. Tattoo complaints and complications: diagnosis and clinical spectrum. Curr Probl Dermatol. 2015;48:48-60.

Uncommon causes of non-melanin pigmentation

Dr. Shivani Bansal
Assistant Professor,
AIIMS Bathinda

CHROMHIDROSIS

Chromhidrosis is a rare condition causing the secretion of coloured sweat. It has been classified into apocrine chromhidrosis, eccrine chromhidrosis, and pseudo-eccrine chromhidrosis. Apocrine chromhidrosis is usually seen after puberty, confined to areas where apocrine glands are present. The sites affected are the face and axilla, anogenital and rarely areola. Lipofuscin granules are responsible for the pigmentation of the sweat seen in apocrine chromhidrosis. Depending on the level of oxidation of the lipofuscin granules in the apocrine glands, the colour of sweat can be yellow, blue, green, and blue-black. It is not influenced by seasonal and geographic factors and has no geographic predisposition. But it relates to emotional stimuli such as anxiety, pain or sexual arousal.[1]

True eccrine chromhidrosis is a less common disorder. Its exogenous causes are colouring of the clear eccrine sweat by ingestion of water-soluble dyes such as tartrazine, flavouring, colouring and additive substances in food products, drugs such as quinine and rifampicin and heavy metal such as copper.[2] The endogenous cause is hyperbilirubinemia associated with liver disorders. Pseudo-eccrine chromhidrosis occurs when the colourless sweat subsequently develops colour on reaching the skin in reaction with exogenous chromogenic bacterial products such as Corynebacterium, bacillus species fungi such as Malassezia furfur, chemicals such as dihydroxyacetone, paints, and dyes.[3]

Differential Diagnosis - The differential diagnosis of chromhidrosis includes bleeding diathesis, hyperbilirubinemia, Addison's disease, hemochromatosis, poisoning and alkaptonuria.

Investigations - Chromhidrosis causes significant embarrassment among patients. A thorough history and physical examination should be done to find the type and cause of chromhidrosis. Examination of the colour of sweat on the

skin and stained cloth should be done under Wood's lamp. Skin biopsies can be done for haematoxylin/eosin staining and fluorescence microscopy to detect and measure lipofuscins within apocrine glands. Spectrophotometer analysis of samples from sweat, sebum, urine, skin scrapings, and extraction samples from clothing can help to aid in the diagnosis. Bacterial and fungal cultures of the skin can be done to rule out pseudochromhidrosis. Other tests include complete blood cell counts to rule out a bleeding diathesis and urinary homogentisic acid level to exclude alkaptonuria.

Treatment - Successful treatment for chromhidrosis remains challenging and is typically focused on ways to reduce secretions. Patients should receive education and reassurance about the condition. Manual pressure can be applied to express apocrine gland contents resulting in an improved appearance for 24 to 72 hours in apocrine chromhidrosis. Other off-label treatments are capsaicin, topical aluminium chloride and injections of botulinum toxin type A. However, relapse can occur. The treatment of eccrine chromhidrosis revolves around stopping the causative agent. In cases of pseudochromhidrosis, topical or systemic antimicrobials are often used to eradicate the offending microorganism.

OCHRONOSIS

The term 'ochronosis' is derived from ochre (as a colour name, 'brownish-yellow). Ochronosis refers to a clinical appearance of blue-black or grey-blue pigmentation, which reflects the histological finding of yellow-brown deposits in the dermis. It can be endogenous and exogenous.

Endogenous ochronosis is the cutaneous manifestation of autosomal recessive inborn error of metabolism, alkaptonuria, which is due to a deficiency of homogentisate 1,2-dioxygenase.[4] The result is systemic sequestration of homogentisate - a colourless phenol that - upon the decay to benzoquinone, can irreversibly bind with collagen. The earliest sign is from parents who notice that their infants' soiled diapers are black in colour. It has predominant musculoskeletal manifestations as early signs and ochronosis involving extra-articular organs such as the eye (ocular pigmentation), skin (pigmentation) particularly the pinna as late signs. Valvular disease and cardiac failure can also be the presentation. These patients excrete homogentisic acid in the urine, which is oxidized by ambient oxygen to benzoquinone acetate, turning the urine dark black. A chromatography assay in the urine for homogentisate is the gold standard for alkaptonuria. Genetic testing can also be done. Treatment options include mega dosing of vitamin C, dietary restrictions of phenylalanine and tyrosine and interprofessional management.

Exogenous ochronosis is an acquired condition resembling clinically and histologically to alkaptonuria but it has no systemic manifestations. It presents as asymptomatic bilaterally symmetrical speckled blue-black macules and several grey-brown macules, previously described as "caviar-like" bodies, typically affecting the malar areas, temples, lower cheeks, and neck.[5] Caviar-like papular and nodular lesions may also be seen (Figure 1). It most commonly results from the use of topical hydroquinone (usually used as bleaching creams) but has also been associated with the use of phenol, quinine injection, resorcinol, picric acid, mercury, and oral antimalarials. The clinical diagnosis may be missed in early stages where it may mimic melasma. It can be seen in all skin

types. Both alcoholic and cream preparations of hydroquinone can cause ochronosis. The lesions may develop gradually over 6 months to 3 years or longer. It can occur at a low concentration as 2% hydroquinone. Multiple theories have been postulated but the most accepted one states that the hyper-pigmentation is due to local competitive inhibition of the enzyme homogentisic oxidase by hydroquinone, which leads to local accumulation of homogentisic acid and its metabolic products that polymerize to form ochronotic pigment in the papillary dermis. Differential diagnosis of exogenous ochronosis includes melasma, nevus of ota, argyria

Investigations - Dermoscopy and reflectance confocal microscopy are non-invasive tools in its diagnosis. Histopathology is the gold standard in the diagnosis depicting its pathognomic histopathological feature of the ochre-coloured, banana-shaped fibers in the dermis.

Treatment - Treatment of exogenous ochronosis is challenging. The first step is immediate cessation of hydroquinone. Various modalities have been described like chemical peels, dermabrasion and laser resurfacing with inconsistent results.[6]

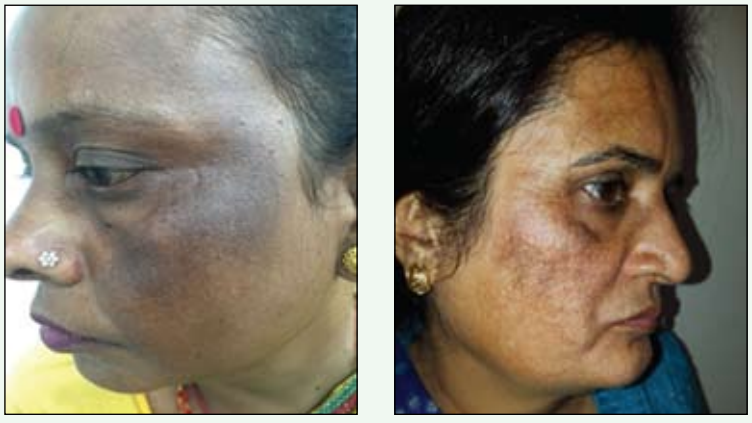


Fig 1 - Cavier like papules with confetti like macules in exogenous ochronosis

References

1. Shah A, Tsianou Z, Suchak R, Mann J. Apocrine Chromhidrosis. Am J Dermatopathol. 2020;42:e147-e148.
2. Hu L, Sun Y. A case of eccrine chromhidrosis: Natural pigment's crime. Australas J Dermatol. 2020;61:e460-e461.
3. Tempark T, Wittayakornrerk S, Jirasukprasert L, Chatproedprai S, Wananukul S. Pseudochromhidrosis: report and review of literature. Int J Dermatol. 2017;56:496-502.
4. Vadera K, Someshwar S, Salunke P. Endogenous Ochronosis: A Rare Entity. Indian Dermatol Online J. 2022; 13:517-18.
5. Lazar M, De La Garza H, Vashi NA. Exogenous Ochronosis: Characterizing a Rare Disorder in Skin of Color. J Clin Med. 2023;12:4341.
6. Qorbani A, Mubasher A, Sarantopoulos GP, Nelson S, Fung MA. Exogenous Ochronosis (EO): Skin lightening cream causing rare caviar-like lesion with banana-like pigments; review of literature and histological comparison with endogenous counterpart. Autops Case Rep 2020;10:e2020197.

Blue lesions on skin- an overview

Dr Rita Vora
Professor & Head,
Pramukhswami Medical College
Karamsad, Gujarat

Dr Pooja Agarwal
Associate Professor,
Smt NHL Municipal Medical College,
Ahmedabad, Gujarat

During daily practise, dermatologists come across a myriad of entities with changes in skin colour. These coloured lesions range from white spots of vitiligo, dark brown lesions of melasma, bluish grey lesions of acquired dermal macular hypermelanosis, reddish lesions of cherry angioma, yellow lesions of xanthelasma to blue lesions like nevus of Ota, to name a few. The present article focuses on the various blue coloured lesions encountered by a dermatologist. The conditions have been classified broadly as nevi, vascular lesions, thermal injury related, infections and infestations, and miscellaneous for easy learning.

1. Nevi

Due to the presence of melanocytes in the dermis and the resultant Tyndall effect, the dermal nevi present with a characteristic bluish hue which is easily recognisable even in the Indian skin.

A. Mongolian spot

They are a very common presentation and are seen as grayish-blue macules of variable sizes present more commonly on the lumbosacral region and buttocks. Less commonly, they may be seen on shoulders, and flanks and are then known as aberrant Mongolian spots. They occur due to an arrest of melanocytes in the deep dermis as they fail to migrate from neural crest to dermoepidermal junction during embryogenesis. Monglion spots usually fade within 2-3 years of life at preschool age but the aberrant ones may persist for life.

B. Nevus of Ota

It is usually congenital but may present later in life also. There is a female predilection. The presenting feature is a unilateral patch of speckled graying-blue discoloration of skin in the region of the ophthalmic and maxillary divisions of the trigeminal nerve, hence the nomenclature nevus fuscoceruleus ophthalmo-maxillaris. The mucosae (conjunctival and nasal) may also be involved. (Fig 1)

Fig 1 – Nevus of ota with conjunctival involvement

C. Nevus of Ito

It has the similar mottled appearance as nevus of Ota and is situated on the supraclavicular, scapular and deltoid regions (nevus fusco caeruleus acromiodeltoideus). Rarely, both nevus of Ota and nevus of Ito co-exist in the same patient.

D. Hori's Nevus

It is a rare form of acquired dermal melanocytosis and was first described by Hori in 1984 as acquired bilateral nevus of Ota like macules (ABNOM). It also goes by the synonyms nevus fusco-caeruleus zygomaticus and acquired circumscribed dermal facial melanocytosis. It presents as multiple bilateral, facial, speckled blue-brown, and/or slate-grey macules occurring bilaterally symmetrically on malar regions or less commonly on the forehead, upper eyelids, cheeks, and nose. It differs from nevus of Ito with its lack of mucosal involvement.

E. Blue nevus: (Blue nevus of Jadassohn–Tièche)

It is a benign tumour of the dermal melanocytes and presents as blue to blue-black, firm papule/ nodule/ plaque, often with an onset during childhood or adolescence. Multiple blue nevi may be associated with the LAMB (lentigines, atrial myxomas, mucocutaneous myxomas, and blue nevi) syndrome.[1]

F. Cellular blue nevus

This is larger than the common type and measures 1-3 cm in diameter. In contrast to the acral location of common blue nevi, cellular nevi are commonly encountered on the buttocks and sacrococcygeal region. Cellular blue nevi-like lesions may also be found on the surface of nevus of Ota and nevus of Ito.

G. Epithelioid blue nevus

This recently described histological variant of blue nevus differs by its propensity to develop at multiple sites and by its distinct histopathology. The epithelioid blue nevus consists of a mixture of highly pigmented globular and fusiform cells with lightly pigmented polygonal and spindle cells. The melanocytes are often scattered as single cells within the collagen bundles.

H. Dermal melanocytic hamartoma

It is characterized by a single, very extensive area of blue discoloration present since birth. Some cases show many macules coalescing, whereas others show widely separated large bluish patches.

2. Vascular lesions

Due to the dermal placement of blood vessels, lesions of dermal vasculature present with a blue hue. Also, bluish lesions are seen in many venous malformations.

A. Blueberry muffin baby

It is the characteristic eruption in neonates reflecting dermal erythropoiesis. The lesions comprise erythematous to bluish purple, circular, or oval macules, papules, and nodules scattered all over the body. It is seen in several congenital infections, notably TORCH infection, Rh incompatibility, ABO blood group incompatibility, hereditary spherocytosis, and twin-twin transfusion syndrome.[2]

B. Blue rubber bleb nevus syndrome:

It is characterized by multiple venous malformations affecting the skin and internal viscera, gastrointestinal tract involvement being the most common. Three types of lesions are described by Bean. First type is compressible, red-blue, nipple-like lesions; second type is blue-black non-blanching macular lesions, and the third type is subcutaneous, vascular, soft tissue lesions. The lesions clinically are characteristically blue/purple soft compressible nodules with a rubbery feel. (Fig 2 3)

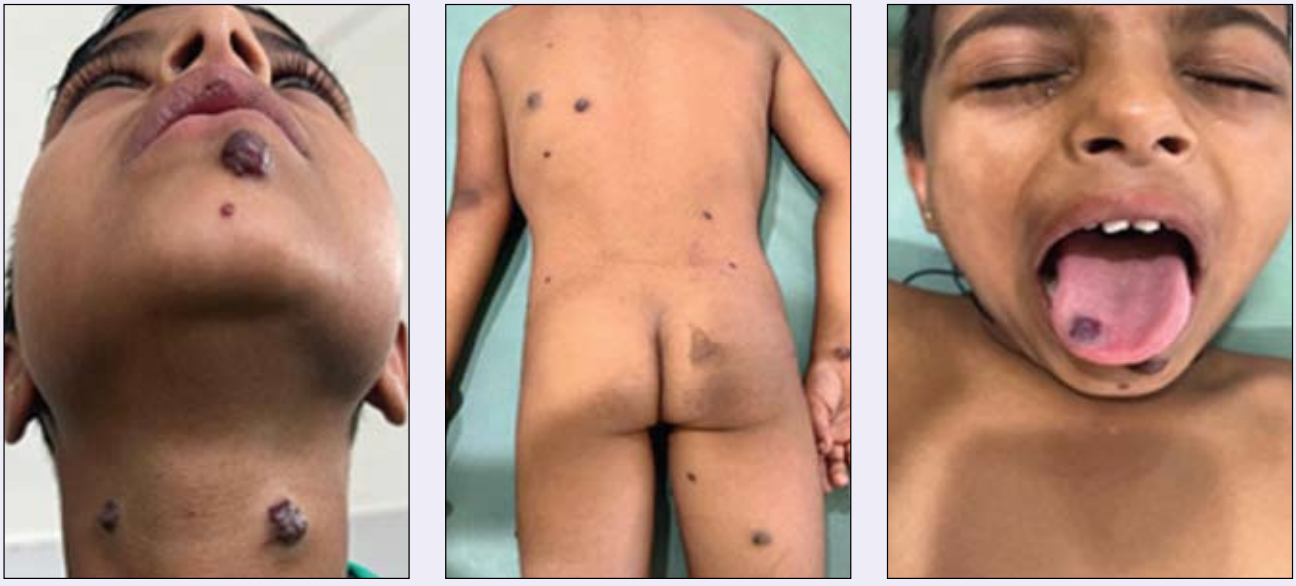


Fig 2 - Blue rubber bleb nevus syndrome

C. Venous malformation

They present as blue to purple grouped spongy nodular lesions at the sites of venous ectases. They may be associated with enlarged neighboring veins, overlying hyperhidrosis, or recurrent thrombophlebitis in or near the lesions. Calcified phleboliths may be present in the lesion. The majority of the lesions are asymptomatic and symptoms occur secondary to pressure on surrounding structures.

3. Thermal injury related lesions

As a result of continuous exposure to cold

temperatures, vasospasm occurs in the dermal vessels with imparts a bluish hue to the skin.

A. **Cutis marmorata -** Newborn infants who are subjected to cooling can develop distinct marbling of the skin. This is a physiological response and it may disappear on rewarming.

B. **Acrocyanosis-** This condition is characterized by deep blue or cyanotic discoloration of the skin over extremities due to vasospasm of cutaneous arteries and arterioles in response to cold or emotional stress. It can be classified as primary (idiopathic/ essential) and secondary. It is seen more commonly in females and presents as persistent, painless, mottled, cyanotic discoloration of the hands, feet and face. The extremities are cold, clammy, swollen and sweaty.

C. **Raynaud's phenomenon -** It is a triphasic change in skin colour due to exposure to cold temperatures. The initial phase of pallor is followed by a blue discoloration and ultimately reddish due. It is best seen over fingers and toes and may be a sign of an underlying autoimmune connective tissue disorder.

D. **Frost bite -** On prolonged exposure to freezing temperature, there is damage to the dermal vascular plexus and the reticular dermis. It is characterised by haemorrhagic blisters associated with skin necrosis and a blue-grey discoloration of the skin followed later by burning, throbbing, and shooting pains.

4. Infections and infestations

A. **Hermans spot and kolpik's spot -** In measles, blue-grey stippling may appear on tonsils (Hermans spot). Punctuate blue-white lesions surrounded by erythematous areola on buccal mucosa against the second molar (Kolpik's spots) are pathognomonic and appear on 2-4 days of fever. Similar spots may be seen at conjunctivae at medial canthi.

B. **Blue ball sign -** In lymphogranuloma venereum, it's a sign of impending rupture where underlying abscess with oedema and livid colour of the overlying skin over bubo is seen.

C. **Maculae ceruleae -** Maculae ceruleae means sky-blue spots. These are bluish macules occasionally seen mailnly on lower abdomen and upper thighs in persons infested with Pthirus pubis. Though very they have been reported secondary to pediculosis capitis bites also.[3]

D. **Blue neck syndrome -** It is a common condition in northern Kerala caused due to a nematode. The affected skin has a dull, dry matt surface with a characteristic bluish-black colour, with distinctive pigmentation of skin folds and surface clearly visible as nonpigmented grooves.

5. Miscellaneous

There are other numerous skin lesions which strictly do not fall under the above headings and have been clubbed together here.

A. **Acquired dermal macular hyperpigmentation -** The entities lichen planus pigmentosus, ashy dermatoses/erythema dyschromicum perstans and Riehl's melanosis/pigmented contact dermatitits are now clubbed together under the umbrella term acquired dermal macular hypermelanosis. It is characterised by small/large patches of blue-gray pigmentation over the trunk, extremities, and neck. (Fig 3)

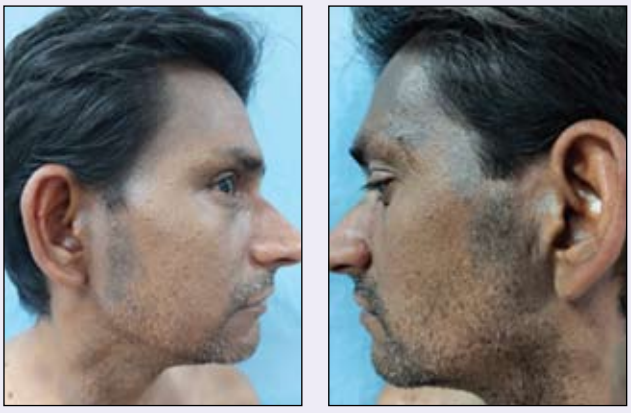


Fig 3 - Bluish grey patches of acquired dermal macular hypermelanosis

B. Blue vitiligo - In vitiligo, sometimes there may be basal cell degeneration due to intense inflammatory infiltrate resulting in presence of melanocytes in dermis. This imparts a bluish hue to the lesion due to the Tyndall effect.[4]

C. Blue sclera - It is seen in patients with Ehlers-Danlos syndrome, pseudoxanthoma elasticum, osteogenesis imperfecta, Marfan's syndrome and Alkaptonuria.

D. Blue man syndrome - It occurs due to excessive exposure to chemical compounds of element silver or silver dust and due to adverse effects of the amiodarone drug. [5]

E. Blue Scrotum Sign of Bryant - JH Bryant described scrotal ecchymosis associated with a ruptured abdominal aortic aneurysm (AAA). Non-traumatic discoloration beneath the intact scrotal or penile epithelium can occur due to blood's extravasation in the retroperitoneum.

F. Blue chromonychia - Blue discoloration of nails is commonly secondary to drugs, most common culprit being minocycline and zidovudine. Chemo-therapeutics like cyclophosphamide, doxorubicin, and bleomycin cocktail therapy may also cause blue chromonychia due to matrix melanocyte activation. Besides drugs, other causes of blue nails include exposure to silver salts either occupationally or as medications, Wilson's disease (causing Azure lunula), glomus tumour of a nail, digital arterio-venous malformation, hereditary acro labial telangiectasia.

G. Ochronosis - It is the bluish gray discolouration of skin and/or cartilages. It may be due to alkaptonuria or secondary to excessive hydroquinone application over face (exogenous ochronosis), Alkaptonuria is an autosomal recessive disorder with decreased production of homogentisic acid oxidase. Homogentisic acid is excreted in urine, small amounts remain in the body and slowly and progressively get deposited in bones, cartilage and skin where it turns into a pigmented polymeric material. The most obvious sign in adults is a thickening and blue-black discolouration of the ear cartilage.

BLUE COLOR IN DERMOSCOPY

With the advent of dermoscopy, it has become easier to study the lesions of the skin. Color in dermoscopy depends on the level where the pigment is located within the skin. Black corresponds to a pigmented cornified layer, whereas blue color corresponds to pigmented structures located in dermis. All the conditions mentioned above will show a blue- bluish grey hue on dermoscopy of the lesions. Only few conditions with certain characteristic features with bluish hue on dermoscopy are described here:

- Blue bleb rubber syndrome: Red-purple globules with verrucous surface with lacunas separated by a white linear structure corresponding to fibrous demarcations. (Fig 4)

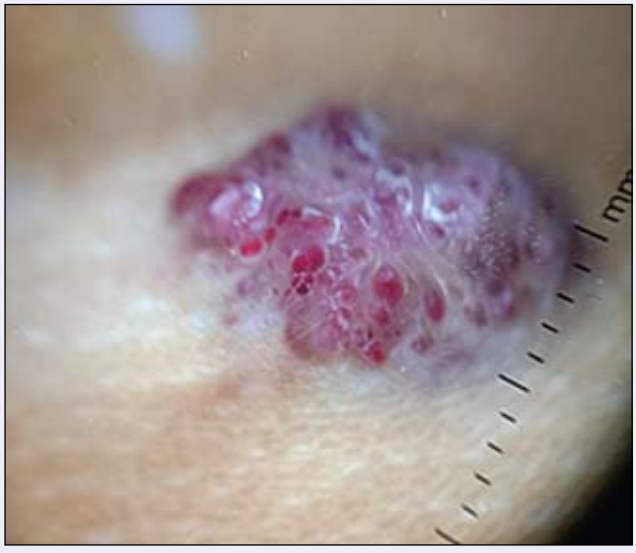
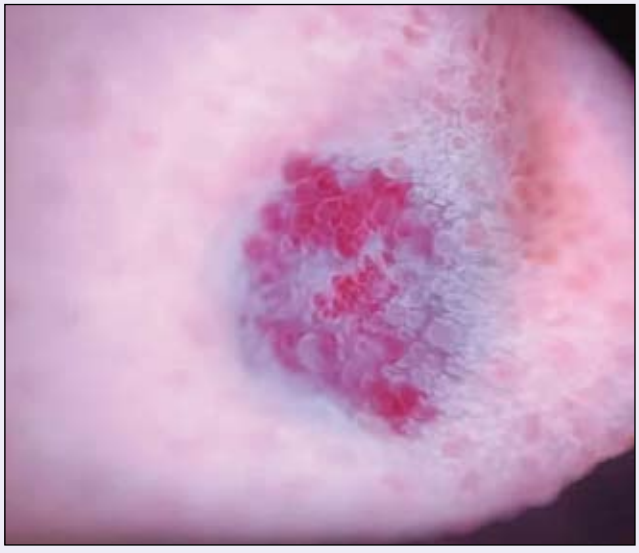



Fig 4 - Dermoscopy of blue rubber bleb nevus lesions

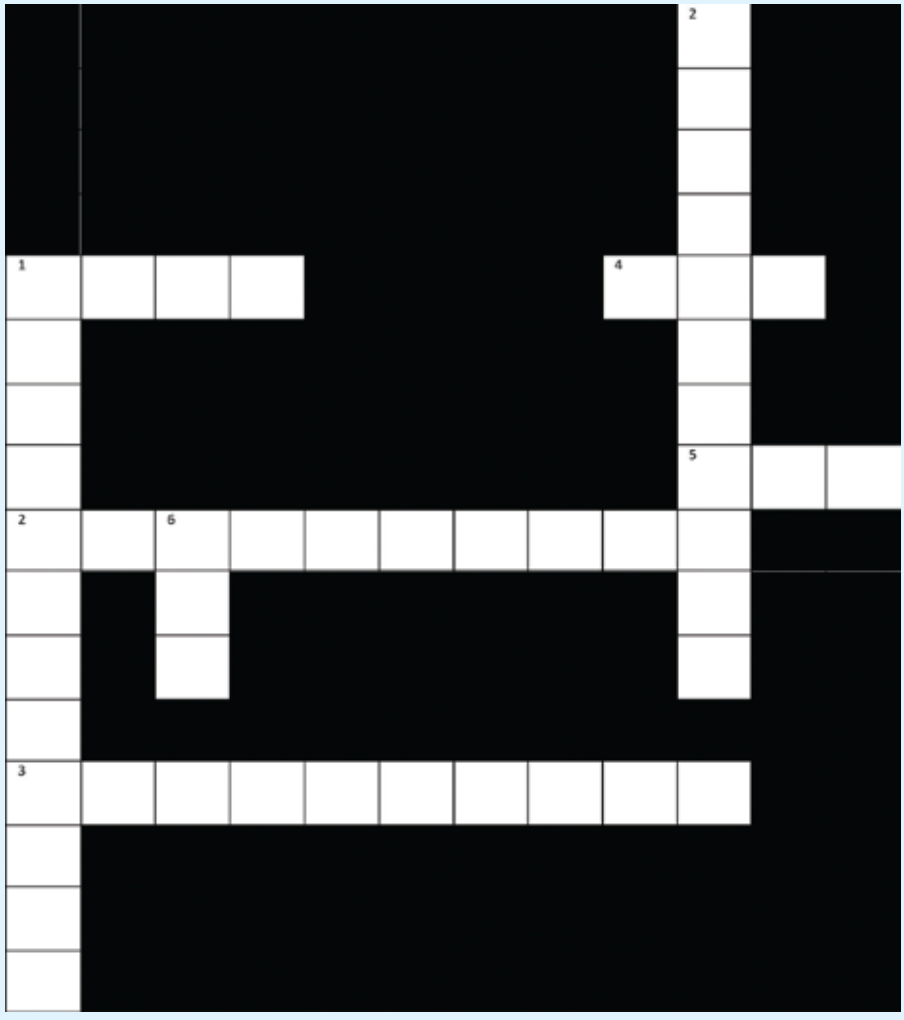
- **Basal cell carcinoma -**
  - o Lesions show blue gray globules/ ovoid nests/ maple leaf pattern with arborizing vessels, blue-white veil, milky red area and ulcerations/crusts.
- **Melanomas -**
  - o Lesions show an atypical pigment network with irregular brown-black dots/ globules and streaks. Pigmentation with multiple colors is asymmetrically distributed. Blue-whitish veil and polymorphic vessels are common in invasive melanoma

References

1. Bolognia JL, Schaffer JV, Cerroni L. Dermatology, 4th Ed, Elsevier Limited, 2018, Chapter 112, p 1963.
2. Christopher Griffiths, Jonathan Barker, Tanya Bleiker, Robert Chalmers & Daniel Creamer, Rook's Textbook of Dermatology,9th Ed, Wiley Blackwell publishing Ltd, 2016, p 116.20.
3. Lokhande AJ, Soni R, Dhali TK. Macula ceruleae with head louse. Indian Dermatol Online J. 2019;10:492–3.
4. Ankad BS, Nikam BP, Jaju PS. Blue vitiligo: A dermascopic perspective. Indian J Dermatol Venereol Leprol. 2019;85:634-7.
5. Fishman TJ, Spencer S, Harrell R, Salabei JK. Amiodarone induced "Blue man syndrome"; an unusual presentation. Heart Lung. 2020;49:202-3.

Non-melanin pigmentary crossword

Dr. Gauri Mahabal
Associate Professor,
Department of Dermatology,
Christian Medical college, Vellore



CLUES

ACROSS

1. A young man treated with minocycline developed blue-black discoloration with acne scars at his cheeks. A Perls stain would show _____ coloured staining granules within macrophages
2. Blue to slate grey skin pigmentation caused by prolonged treatment with gold salts is called as _____
3. A dermatopathologist receives a skin biopsy sample from the scapular area of a 35-year-old female presenting with hyperpigmented, thin plaques, containing "rippled" linear gray-tan streaks, with history of use of bath loofahs. Which fluorescent stain can help in the identification of the etiological agent?_____
4. A 45-year-old Caucasian male presents with cirrhosis, diabetes mellitus, and bronze discoloration of the skin. Which is the most likely genetic defect responsible for this condition? _____
5. The mother of a four-month-old female child presented with a history of black staining of the diaper after few minutes of urination. Which is the most likely enzyme deficiency responsible for this condition? _____

DOWN

1. Yellowish orange pigmentation of the skin starting over the palms, soles, forehead, tip of the nose, and nasolabial folds and progressing gradually over the entire body, with sparing of the sclera and mucous membranes. Ingestion of which nutrient is most likely responsible for this condition
2. A 16-year-old boy presented with yellowish brown coloured sweating in his armpits, which stained his clothes, and was often provoked by stress. Histopathological staining of skin biopsy from his axillae will show an increased _____ pigment in the cytoplasm of the apocrine glands
6. Which colour tattoo is most prone to developing allergic reactions?

ANSWER KEY

ACROSS : 1 - BLUE, 2 - CHRYSIASIS, 3 - THIOFLAVIN, 4 - HFE, 5 - HGD

DOWN : 1 - BETA-CAROTENE, 2 - LIPOFUCHSIN, 6 - RED

CASE VIGNETTE

Dr. Pragya Nair
Professor, Department of Dermatology, Pramukhswami medical college, Shree krishna hospital, Bhaikaka University Karamsad, Gujarat

A 20-year-old female presented with complaints of yellowish discoloration of skin for 1 month, aggravated on exertion. She also complained of yellowish staining of the clothes. There was no history of ingestion of any drugs, foods rich in carotene such as carrots, citrus fruits, or sweet potatoes.

She denied contact with yellow colored products in the form of any chemicals, dyes, deodorants, cosmetics or colored clothes. No history of specific odour and no underlying psychiatric ailment could be elicited . No similar complaints in the past or in the family.

On dermatological examination, yellowish skin over the palms and forearm, toe webs, and face.Axillae and groins were normal. Wood's lamp examination showed yellowish florescence over face and palms. Blotting sweat with a white cloth showed yellow stain. The color of her tears, saliva, and urine was unchanged. Routine laboratory investigations were normal.Microscopy and culture of skin scraping were negative for fungus and bacteria.Skin biopsy was negative for lipofuscin granules. Patient responded to oral antibiotic and use of antiseptic soap.

What is the diagnosis ?

Pseudochromhidrosis

It is also known as extrinsic chromhidrosis, a condition in which normal colorless sweat becomes colored because of the presence of chromogens, such as chromogenic bacterial products (e.g., those of Corynebacterium species), chemicals, heavy metal paints, or clothing dyes, and self-tanning products when it reaches the skin.

Corynebacteria are responsible for red pseudochromhidrosis, whereas Malassezia furfur and Bacillus species are the agents involved in the blue pseudochromhidrosis. The ecological stability of these commensal bacteria in different body sites rely on environmental factors such as hydration, oxygen, growth substrates, and the pH of the stratum corneum.

There are case reports of pseudo chromhidrosis with reddish

pigmentation where no organism was isolated in the culture but were successfully treated with oral and topical antibiotics. Pseudochromhidrosis needs to be differentiated from apocrine and eccrine chromhidrosis because it is important for the prognosis. The differential diagnosis for skin and sweat pigmentation includes hyperbilirubinemia, hematohidrosis (sweats blood), alkaptonuria, copper exposure, Addison disease, and hemochromatosis.

Fungal and bacterial cultures of the skin should be performed to eliminate the cause of mere pseudochromhidrosis. Treatment for pseudochromhidrosis is successful with antibiotics and cessation of the offending agent, it can be a cause of embarrassment for patients and can be frustrating for healthcare provider and patients both.

The initial assessment of a patient who presents with pigmented sweat should include detailed history with careful attention toward any new medications started close to the onset of the symptoms, including herbal medications, vitamins, and other supplement. A thorough psychiatric evaluationwas done by a psychiatrist to rule out any psychiatric ailment as it has an impact on psychological stress and social embarrassment. Present case showed yellowish discoloration of the skin, was also negative for organisms on culture, but improvement with oral erythromycin and topical antiseptic soap shows bacterial etiology

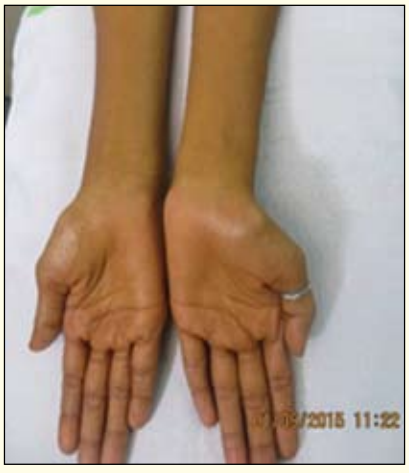


Fig 1: Yellowish discoloration of face and extremities

Fig2: Yellowish florescence under Wood's lamp

Fig 3: Yellowish staining of clothes

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