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Review Article

Acquired macular hyperpigmentation an overview

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Abstract Acquired hyperpigmentation is always difficult to diagnose and more difficult to treat satisfactorily. There are many conditions which need to be considered before making a diagnosis of acquired macular hyperpigmentation like erythema dyschromicum perstans, lichen planus pigmentosus, macular amyloidosis, tar and frictional melanosis, post-inflammatory hyperpigmentation, Berloque dermatitis, Riehl's melanosis and drugs and chemicals.

Key words
Acquired hyperpigmentation, Berloque dermatitis, Riehl's melanosis, erythema dyschromicum perstans

Introduction

Hyperpigmentation in general is due to, increased melanin production by existing melanocytes or from increased proliferation of active melanocytes. Hyperpigmentary skin disorders are defined as 'increased pigmentation of the skin and mucous membranes to the extent that the patient concerned seeks medical advice'. These skin disorders may be classified as epidermal and dermal hyperpigmentaion, depending on the location of the pigments. Epidermal hyperpigmentation is because of melanin pigmentation and has a brownish hue. Dermal pigmentation is called 'ceruloderma' or 'blue hyperpigmentation' which may either be due to melanin or due to non-melanin pigments.

Differential diagnosis of acquired hyperpigmented macules is endless. The most common dermatological causes of acquired hyperpigmented macules in clinical practice are, **(Table 1)**

1. Erythema dyschromicum perstans
2. Lichen planus pigmentosus
3. Macular amyloidosis
4. Friction melanosis
5. Tar melanosis
6. Berloque dermatitis
7. Riehl's melanosis
8. Idiopathic eruptive macular pigmentation
9. Post-inflammatory hyperpigmentation
10. Hyperpigmentation due to drugs and heavy metals

Erythema dyscromicum perstans (EDP)

Synonyms Ashy dermatosis of Ramirez, dermatosis cenicientos, erythema chronicum, figuratum melanodermicum

It is an idiopathic, acquired, generalized, macular ashen-grey-blue hypermelanosis which

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Table 1 Differentiating above conditions

Condition	*Age*	*Sex*	*Etiology*	*Clinical features*	*Histopathology*
Erythema dyschromicu n perstans	Any age	Both F>M	Unknown. ?Ammonium nitrate, whip worm, contrast media.	Ash-coloured, polycyclic macules with elevated borders (piece of string) over trunk, arms, face	Non-specific. Mild basal cell degeneration with perivascular mononuclear cell infiltrate
Lichen planus pigmentosus	Any age	Both F>M	Unknown. ? HBV, HCV.T-Lymphocytic abnormality	Discrete dark brown macules over trunk, extensor aspect of arms with pruritus	Atrophic epidermis, vacuolar degeneration of basal cell layer with lichenoid infiltrate of upper dermis
Macular amyloidosis	Adults	F>M	Constant rubbing with nylon brush or towel	Pruritic, dusky brown or grayish pigmented macules in a rippled pattern over upper back, arms, legs	Globular, amorphous amyloid deposits seen in dermal papillae. Congo red stain positive.
Friction melanosis	Any age	Both	Chronic constant friction, pressure or irritation by nylon and cotton towels, sponges, brushes	Pigmented reticulated macules over clavicle, knees, elbows, ribs	Flattened epidermis with isolated necrosis of keratinocytes and areas of the cleavage of the dermo-epidermal junction leading melanin incontinence
Tar melanosis	Adults	M>F	Exposure to coal tar, mineral oils and hydrocarbons	Asymptomatic small bluish-grey hyperpigmented macules which often merge with each other to form large confluent areas involving face, trunk and extremities	Follicular hyperkeratosis, reduced basal cell pigmentation, pigmentary incontinence and perivascular lymphocytic infiltration
Berloque dermatitis	Adults	Both F>M	Exposure to bergapten, or 5-methoxypsoralen, is the photoactive component of bergamot oil from the bergamot lime (*C bergamia*), which is a popular ingredient in perfumes and fragrances.	Brown hyperpigmentation with or without preceding erythema is seen in a droplike or pendantlike configuration. Seen over the sides of the neck in adult females, although it may be seen in any part of the body where perfume was applied followed by sun-exposure.	The epidermal changes consist of keratinocyte necrosis, intercellular and intracellular edema, and intraepidermal blisters. Dermis shows mild perivascular infiltrate.
Riehl's melanosis	Middle age	F>M	Exposure to formaldehyde, brilliant lake red R, musk ambrette, aniline dyes.	Diffuse or patchy brown pigmentation on the cheeks and the forehead seen. It is more intense on the forehead and the temples, and severe cases may look black, purple, or blue-black.	Interface changes occur with liquefactive basal cell degeneration. A moderate lymphohistiocytic infiltrate is present in the upper dermis, mainly in a perivascular distribution.
Idiopathic eruptive macular pigmentation	Puberty	M=F	Hormonal factors may play a role as the condition is seen in the peripubertal age group.	Aymptomatic pigmented macules that involve the face, trunk and proximal extrmities. These occur in crops and gradually resolve over months to years without any scarring and residual pigmentation	Epidermal hypermelanosis with increased melanin in the basal layer of the epidermis and variable dermal inflammation and melanophages in the dermis

Cont..

Condition	*Age*	*sex*	*Etiology*	*Clinical features*	*Histopathology*
Postinflammatory pigmentation	Any age	F=M	Allergic reactions, infections, trauma, and phototoxic eruptions. Acne excoriée, lichen planus, systemic lupus erythematosus, chronic dermatitis, and cutaneous T-cell lymphoma, especially erythrodermic variants	The distribution of the hypermelanotic lesions depends on the location of the original inflammatory dermatosis. The color of the lesions ranges from light brown to black, with a lighter brown appearance if the pigment is within the epidermis and a darker gray appearance if lesions contain dermal melanin	Epidermal PIH involves increased melanin pigment in the basal cell layer of the epidermis. Dermal PIH involves the upper dermis, with pigment incontinence due to increased numbers of melanophages in the papillary dermis.
Pigmentation due to drugs/Heavy metals	Any age	F=M	Amiodarone, antimalarials, bleomycin, busulfan, cyclophosphamide, dactinomycin, daunorubicin and 5 FU, Minocycline Chlorpromazine, Bismuth, gold, mercury, silver	Amiodarone - slate-grey, Antimalarials - yellow-brown, Bleomycin - flagellate hyperpigmention, Minocycline - grayish discolouration, Gold – blue-grey deposits around eyes, Silver - diffuse slate-grey discolouration of sun-exposed areas.	Increased melanin in the epidermis (tends to be more brown, hence 'hyperpigmented'), melanin in the epidermis and high dermis (mostly brown with hints of grey or blue), increased melanin in the dermis (tends to be more greyish or blue), and dermal deposition of the drug or metabolite (usually slate or bluish grey).

occurs in otherwise healthy individuals. Lesions begin as erythematous macules, which later develop a slate-grey or ashen hue **(Figure 1)**. Usually the lesions are flat but active lesions may have a slightly raised, erythematous border like 'a thin piece of string'. Lesions are usually numerous and may vary in size from few millimeters to many centimeters and have a tendency to coalesce and cover extensive areas of trunk, limbs and face. They have not been found on the soles, palms, nails or the mucous membrane. They are usually asymptomatic.

The etiology of EDP is unknown and is not associated with any internal condition, although isolated reports of ammonium nitrate ingestion[1,9,10] and whipworm (*Trichuris trichiura*) infestation[2] have been suggested to be the cause.

Histopathology

In the early active stage, many basal cells and some squamous cells in the lower epidermis show vacuolization of their cytoplasm. This leads to liquefaction degeneration. The upper dermis shows a mild to moderate perivascular infiltrate. This infiltrate consists of lymphocytes and histiocytes intermingled with melanophages. Occasional colloid bodies, resembling those seen in lichen planus, may be present.

Damage to basal layer, resulting in formation of colloid bodies and pigmenting incontinence, suggests a possible relationship of EDP to lichen planus pigmentosus.[15,3] It is true that lichen planus pigmentosus has a more pronounced lichenoid infiltrate and its lesions have a greater predilection to be located in the exposed areas but the occasionally described coexistence of

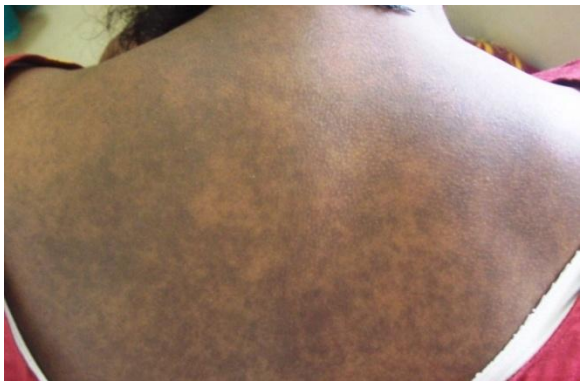

Figure 1 Slate-grey coloured macules of erythema dyschromicum perstans.

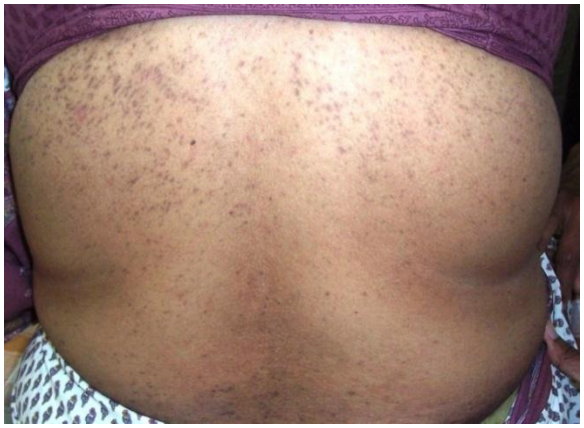

Figure 2 Brownish-black macules of lichen planus pigmentosus.

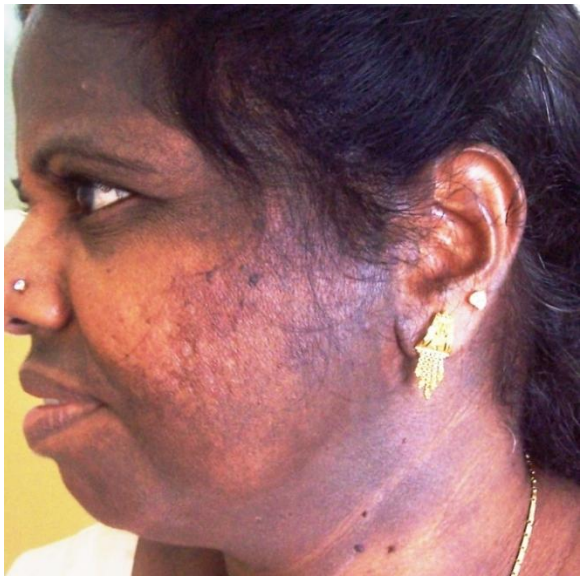

Figure 3 Bluish-grey hyperpigmented macules over face.

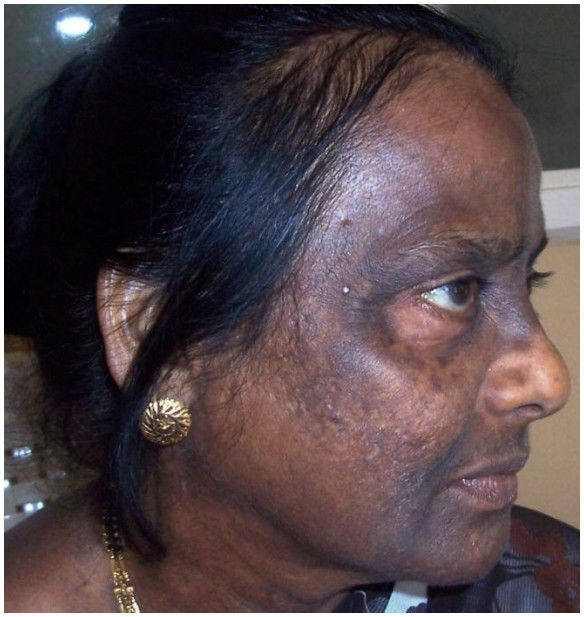

Figure 4 Brownish macules over face.

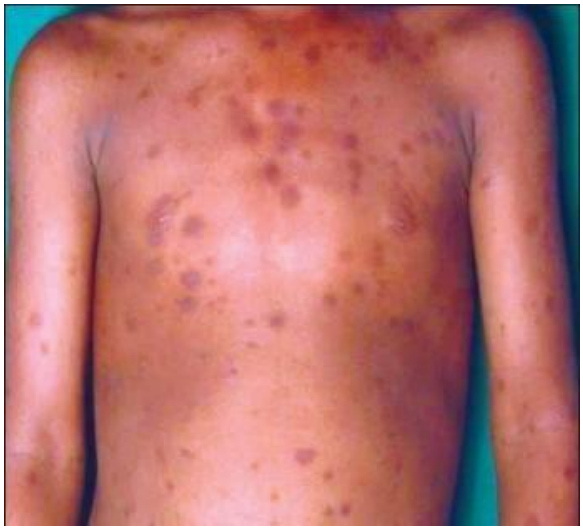

Figure 5 Pigmented macules of idiopathic eruptive macular pigmentation.

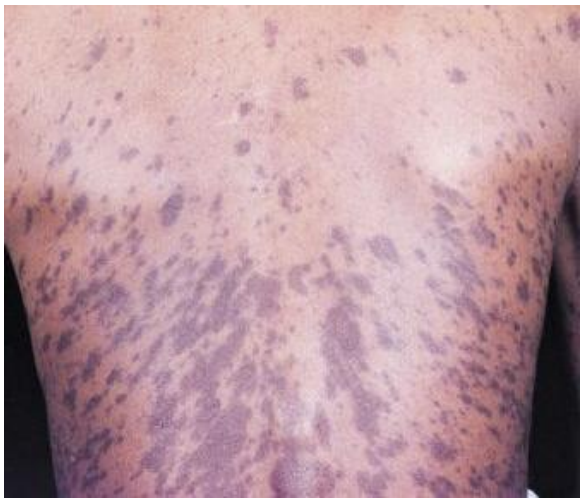

Figure 6 Hyperpigmented macules over trunk due to psoriasis.

the two conditions suggests that they are related.

Treatment

Many therapeutic options are available, but few have been effective, except for clofazimine. Clofazimine is a lipophilic rhimophenazine dye with both antimicrobial and anti-inflammatory properties originally developed to treat tuberculosis. Although its mechanism of action is unclear, it seems to exert its main effect upon neutrophils and monocytes in a variety of ways, such as stimulating phagocytosis and release of lysosomal enzymes.

Clofazimine is administered orally, with improved bioavailability when taken with food. It concentrates in lipid-rich tissues, including the reticuloendothelial system, the intestine, the breasts, and the liver. Its half-life is 70 days. Isoniazid increases its serum levels and enhances its urinary excretion. Its most common adverse effects are in the skin, the gut, and the eye. It gives a temporary orange discoloration of the skin and the eye (ie, cornea, conjunctivae); it also may produce ichthyosis. Its most serious adverse effect is crystal deposition in the gut that produces a potentially fatal enteropathy. This rare complication is associated with months of high-dose (>100 mg/day) therapy. Nausea and diarrhea are more common. Splenic infarction and eosinophilic enteritis are also rare adverse effects.

Many other therapeutic modalities have been attempted, none with satisfactory results. These include dapsone, ultraviolet exposure, ultraviolet avoidance, antibiotics, antihistamines, griseofulvin, chemical peels, antibiotics, corticosteroids, vitamins, isoniazid, chloroquine, and psychotherapy.

Lichen planus pigmentosus (LPP)

Synonym Invisible pigmented lichen planus.

It was described in 1956 by Shima *et al*. Lichen planus pigmentosus is characterized by discrete dark brown macules with non-characteristic distribution that predominates in exposed areas and flexor folds.[3,14,11] It commonly occurs on the trunk and extensor aspect of arms. Its evolution is characterized by exacerbations and remissions. In some cases there may be associated pruritus. The lesions characteristically spare the muocus membranes, palms and soles. In a study by Kanwar, in 124 Indian patients with lichen planus pigmentosus, the face and neck were the commonest sites affected with pigmentation varying from slate grey to brownish-black. The pattern of pigmentation was mostly diffuse (77.4%) [**Figure 2**], followed by reticular (9.7%), blotchy (7.3%) and perifollicular (5.6%). Lichen planus was noted in 19 patients with typical histopathological changes of the disorder.

The histopathologic picture of LPP shows an atrophic epidermis with vacuolar degeneration of the basal cell layer. In the dermis, a scarce lymphohistiocytic or lichenoid infiltrate and pigmentary incontinence with melanophages can be found.

Treatment

It has a prolonged course and resistant treatment. Potent and moderately potent steroids were tried. It is resistant to tacrolimus also. Vitamin A has been tried successfully in the treatment of LPP.[18]

Macular amyloidosis

It is a form of primary localized cutaneous amyloidosis. The main feature of primary cutaneous amyloidosis is the accumulation of

amyloid in previous apparently normal skin without any deposits in the internal organs.

Macular amyloidosis (MA) is the most subtle of the cutaneous amyloidosis. The original description of this entity was made by Palitz and Peck in 1952. It is more common among central and south Americans, middle easterns and Asians who have dark skin. It is rare among European and North American races.

Amyloid deposits in MA bind to antikeratin antibodies. These deposits contain sulfhydryl groups pointing to altered keratin as a source for these deposits. Apaydin *et al*. found no differences in staining characteristics of cytokeratins between MA. Interestingly, in their study, all the cytokeratins detected in amyloid deposits were of basic type (type II). This may be because, in amyloidogenesis, acidic cytokeratins such as cytokeratin 14 are degraded faster than basic types.

The exact origin of amyloid deposits in MA has not been determined. Two theories have been proposed to explain the origin of the amyloid deposits. These theories are not mutually exclusive, and both could be possible.

Fibrillar body theory

This theory proposed by Hashimoto suggests that the necrotic epidermal cells (colloid bodies) are transformed into amyloid by dermal macrophages and fibroblasts by a process called filamentous degeneration. The absence of amyloid deposits in other dermatoses with colloid bodies (e.g. lichen planus) is explained by the brisk inflammatory reaction clearing them promptly in lichen planus, while the lack of inflammatory cells leads to the formation of amyloid deposits in MA. This theory does not explain how the alpha type of keratin tertiary structure is degraded and converted into the beta-pleated sheet configuration of amyloid.

Secretory theory

This theory proposed by Yamagihara *et al*. suggests that the amyloid in MA is secreted by disrupted basal cells and is assembled at the dermoepidermal junction (DEJ).

Clinical features

The lesions consist of macular hyperpigmented areas predominantly on the upper back (interscapular area), buttocks, chest (over clavicles, on the ribs), breast and extremities (shins and forearms). Lesions appear as grayish-brown macules, 2-3 mm in diameter. A reticulate or 'rippled' pattern of pigmentation is a characteristic diagnostic feature in many cases of macular amyloidosis. Macules may have mild to moderate pruritus. Sometimes pruritus may be absent.

The condition usually presents in early adult life and persists for many years. Both sexes may be equally affected. Macular and lichen amyloidosis frequently coexit giving evidence to the concept of biphasic amyloidosis.

Histpathology shows amyloid deposited in and confined to the papillary dermis and does not extend beyond the subpapillary plexus. When routine stains are used, amyloid has amorphous, glassy appearance. Amyloid exhibit green birefringence with Congo red when viewed under polarizing microscope. This is because of perpendicular arrangement of fibrillary deposits. Fluorescent stains like thioflaine-T can also be used to demonstrate amyloid. Other stains used are methyl violet, cresyl violet,[2,13] periodic acid-sciff **(**PAS), van Gieson's, pagoda red, RIT scarlet No 5, RIT cardinal red No 9 and dylon.

Direct immunofluorescence usually reveals focal Ig G, Ig M and C3.

Treatment

Sedating antihistamines have been found to be moderately effective. Topical dimethyl sulfoxide (DMSO), a chemical solvent, and intralesional steroids are beneficial if combined with other modalities. DMSO has been used with moderate success, but failures have also been reported. Pandhi *et al*. reported a lack of effect with DMSO treatment for cutaneous amyloidosis. Treatment with ultraviolet B (UV-B) light can provide symptomatic relief.

Friction melanosis

It is characterized by hyperpigmentation over bony prominences, secondary to the friction associated during showering.[4] It may be due to prolonged mechanical friction pressure or chronic irritation. The tools used for causing friction may be nylon towels, sponges, cotton towels, brushes and back scratchers etc. Race seems to be important because it is common disorder among Japanese and Latin Americans who share similar skin color.

Clinical examination reveals well-circumscribed reticulated macules. It is localized in the clavicular zones, trunk (mainly over scapular areas), neck, knees, elbows, ribs and extremities. Lesions are usually asymptomatic and they have a chronic indolent course. Though the pathogenesis of this condition remains unclear, it seems likely that it is due to prolonged mechanical friction, pressure and chronic irritation as they appear over osseous prominences. Another factor of this pigmentation is contact dermatitis to components of nylon such as phenol, formalin, mercuric chloride, phenylmercuric acetate and formaldehyde.

Histologically, there is flattened epidermis with isolated necrosis of keratinocytes and micrscopic areas of the cleavage of the dermo-epidermal junction which lead to incontinence of pigment in the form of free melanin in the dermis or within the dermal macrophages.

Treatment

Removal of the cause is the main treatment. Patients should avoid rubbing the skin with nylon towels, sponges, cotton towels, brushes and back scratchers etc.

Tar melanosis

Tar melanosis has also been called occupational melanosis, melanodermatitis xerotica or toxic melanodermatitis. This is commonly encountered among workers with tar, coal tar products, mineral oils and other hydrocarbons. Substances in coal tar with phototoxic properties are anthracene, benzpyrine, acridine, phenanthrene, pyridine etc.

Tar melanosis is characterized by the development of asymptomatic small bluish-grey hyperpigmented macules which often merge with each other to form large confluent areas involving face **(Figure 3)**, trunk and extremities and lesions of the forearm and legs tend to be perifollicular. In early stages there is erythema, edema, vesiculation and pruritus. Later, cutaneous hyperpigmentation in a reticulate pattern gradually develops with variable degree of atrophy, telangiectasia, scaling and follicular keratosis.

Histological examination reveals follicular hyperkeratosis, reduced basal cell pigmentation, pigmentary incontinence and perivascular lymphocytic infiltration.[2]

Treatment

Avoidance of the exposure to tar and tar containing products helps in the improvement of pigmentation. Any pigment reducing substances like hydroquinone, glycolic acid, azaelic acid or kojic acid can be used.

Berloque dermatitis

Synonym Photocontact dermatitis

Phototoxicity or photoirritation is a chemically induced nonimmunologic acute skin irritation requiring light (usually within the UVA spectrum, ie, 320-400 nm). The skin response resembles exaggerated sunburn and does not require prior sensitization; it can be caused by a single simultaneous exposure to the chemical and light source. The photoactive chemical may enter the skin via topical administration, or via ingestion, inhalation, or parenteral administration. The reaction can be evoked in all subjects as long as the concentration of the chemical and the dose of light are sufficient.

In the case of berloque dermatitis, the phototoxic reaction is induced by the effect of long-wave ultraviolet (UVA) radiation on bergapten, or 5-methoxypsoralens, a furocoumarin now known to be the only photoactive component of bergamot oil. The bergapten-UVA radiation combination induces an intensification of melanogenesis and a corresponding increase in the number of functional melanocytes, which are more dendritic and dopa-positive. The distribution of melanosomes in keratinocyte changes from the aggregate to nonaggregate form.

Hyperpigmentation is rarely preceded by erythema, pruritus or a severe phototoxic reaction. There is rarely any inflammatory phase. Following light exposure, there will be development of deep brown cutaneous pigmentation over the primary sites of application of the perfume and along the course of its subsequent trickling. Because the perfume is often applied to the chest, the ensuing photodermatitis which resembles a pendent, was referred to as 'necklace dermatitis'.

Treatment

The primary aim of the therapeutic regime is discontinuation of the offending substance. If berloque dermatitis is the putative diagnosis, all bergamot oil-containing perfumes should be avoided. Any perfumes that are worn should be worn on covered-up areas, not on areas of sun exposure.

If the patient presents in the acute phase and is in considerable discomfort, wet compresses may be helpful in relieving the discomfort. Simple analgesia may be given if the patient is in pain.

For secondary hyperpigmentation, the natural course of the dermatitis is spontaneous resolution after several months, but some lesions may persist much longer. The most important step is to minimize exposure to the sun. This may be done by avoiding strong sunlight whenever possible, avoiding the use of sunbeds and using a strong sunscreen (SPF 30 or higher) with activity in both the UVA and UVB spectra. Camouflage also may be used on exposed hyperpigmented areas, for cosmetic reasons.

If the pigmentation is persistent, hydroquinone constitutes the mainstay of medical therapy. It usually is given twice a day, at a concentration of about 2%, for several months. At higher concentrations, the patient would be at risk of irritation. Hydroquinone sometimes is administered in conjunction with topical tretinoin (Retin-A). Kligman and Willis devised a concoction known as Kligman's formula,

consisting of hydroquinone, tretinoin, dexamethasone, ethanol, and propylene glycol, which they found effective in treating hyperpigmentation.

A novel therapy for pigmentary disorders is ellagic acid, now commercialized in Japan. Ellagic acid is a naturally existing polyphenol that inhibits tyrosinase activity by chelation of the copper ion at the active center of the enzyme.

Riehl's Melanosis

Riehl melanosis is a nonpruritic pigmentary dermatosis affecting the face. It was first observed in 1917. It is characterized by brownish grey facial pigmentation that is more marked on the temples and the forehead. Riehl's melanosis was later noted to occur in people with dark complexions in whom hyperpigmentation with pigment incontinence may be the main sign of contact dermatitis caused by certain allergens. Today, Riehl melanosis is almost synonymous with pigmented contact dermatitis of the face, the most common causes of which are sensitizing chemicals in cosmetics.

Clinical feature

Riehl's melanosis is characterized by reticular, black to brown, violet pigmentation of the face**.**[2] Pigmentation is more intense on the forehead, zygomatic and/ or temporal regions **(Figure 4)**. Pigmentation may extend to the chest, neck and scalp. Various etiological factors have been incriminated for Riehl's melanosis. The disease has also been called as 'war melanosis' because of its occurrence during and after both world wars. This was attributed to exposure to tar. The disease was called 'Pigmented contact dermatitis' by Nakayama.[5,12] Although the etiology remains unsettled, Riehl's melanosis may be a result of contact sensitivity or photocontact dermatitis related to a chemical, particularly a fragrance, found in cosmetics.

Histologically, in the early stages there is liquefaction degeneration of the basal layer of epidermis and a perivascular or band-like dermal infiltrate. There is also pigmentary incontinence. Later, the epidermis appears normal, but many melanophages are present in the upper dermis.

Treatment

Avoidance of the allergen is necessary when it is identified. UV light may have a role to play; theoretically, some patients may benefit from sun avoidance and sunblocks where photoaggravation is established. No effective treatment/cure of Riehl's melanosis has been reported.

Idiopathic eruptive macular pigmentation (IEMP)

Idiopathic eruptive macular pigmentation (IEMP) is a benign, self-limiting melanosis commoly occurs in children and adolescents. It is characterized by the presence of asymptomatic pigmented macules that involve the face, trunk and proximal extremities **(Figure 5)**.[7,16] These occur in crops and gradually resolve over months to years without any scarring and residual pigmentation. The first description was by Degos *et al*.[6] in 1978 in French while in English was by Sanz de Galdeano *et al*. in 1996. Histopathologically, IEMP is an epidermal hypermelanosis with increased melanin in the basal layer of the epidermis and variable dermal inflammation and melanophages in the dermis. Although these are not specific, biopsy is important to exclude the other conditions, which clinically resemble it. The pathogenesis is not known and it is possible that hormonal factors

may play a role as the condition is seen in the peripubertal age group.

Treatment

Active treatment of this asymptomatic condition is unnecessary as it spontaneously resolves within months to years.

Post-inflammatory hyperpigmentation

Post-inflammatory hyperpigmentation (PIH) is caused by 1 of 2 mechanisms that result in either epidermal melanosis or dermal melanosis. The epidermal inflammatory response (i.e. dermatitis) results in the release and subsequent oxidation of arachidonic acid to prostaglandins, leukotrienes, and other products. These products of inflammation alter the activity of both immune cells and melanocytes. Specifically, these inflammatory products stimulate epidermal melanocytes, causing them to increase the synthesis of melanin and subsequently to increase the transfer of pigment to surrounding keratinocytes. Such increased stimulation and transfer of melanin granules results in epidermal hypermelanosis. On the contrary, dermal melanosis occurs when inflammation disrupts the basal cell layer, causing melanin pigment to be released and subsequently trapped by macrophages in the papillary dermis, also known as pigmentary incontinence

PIH can occur with various disease processes that affect the skin. These processes include allergic reactions, infections, trauma, and phototoxic eruptions. Fractional laser photothermolysis occasionally induces PIH. Common inflammatory diseases that result in PIH include acne excoriée, lichen planus, psoriasis **(Figure 6)**, systemic lupus erythematosus, chronic dermatitis, and cutaneous T-cell lymphoma, especially erythrodermic variants. Furthermore, lesions of PIH can darken with exposure to UV light and various chemicals and medications, such as tetracycline, bleomycin, doxorubicin, 5-fluorouracil, busulfan, arsenicals, silver, gold, antimalarial drugs, hormones, and clofazimine.

Treatment

A variety of topical treatments have been used to treat epidermal PIH, with varying degrees of success. These agents include hydroquinone, tretinoin cream, corticosteroids, glycolic acid (GA), and azelaic acid. Topical tretinoin 0.1% has been effective in African Americans. GA peels, in combination with tretinoin and hydroquinone, are an effective treatment of PIH in dark-complexioned individuals. After sufficient improvement of the hyperpigmentation is achieved, a corticosteroid may be applied topically with hydroquinone to promote healing. This combination of various topical therapeutic agents has been shown to be beneficial, especially on the face.

Topical azelaic acid, which has been approved for the treatment of acne vulgaris, is useful for postinflammatory hyperpigmentation. Other treatment modalities include use of trichloroacetic acid and gentle cryotherapy with liquid nitrogen. Each method must be used with extreme caution to avoid necrosis or blistering of the treated skin. These 2 methods of treatment should be avoided in dark-skinned patients because of the risk of permanent depigmentation and scarring.

Hyperpigmentation due to drugs and heavy metals

Mechanisms include increased melanin in the epidermis (tends to be more brown, hence hyperpigmented), melanin in the epidermis and high dermis (mostly brown with tints of grey or blue), increased melanin in the dermis (tends

Table 2 Morphology of drug induced hyperpigmentation

Drug	*Pattern of pigmentation*
Amiodarone	Slate-gray to violaceous pigmentation of sun exposed areas
Antimalarials	Yellow-brown to bluish black discolouration of pretibial region, face, oral cavity
Bleomycin	Flagellate hyperpigmented streaks on the back
Busulfan, cyclophosphamide, dactinomycin, daunorubicin and 5-fluorouracil	Diffuse hyperpigmentation
Minocycline	Greyish discolouration of teeth, nails, sclera, oral mucosa.
Chlorpromazine	Greyish blue discolouration of sun-exposed areas
Heavy metals	
Bismuth	Blue-grey discolouration of face, neck and hands
Gold	Blue-grey deposits around eyes
Mercury	Slate-grey discolouration of skin folds
Silver	Diffuse slate-grey discolouration of sun-exposed areas

to be more greyish or blue), and dermal deposition of the drug or metabolite (usually slate or bluish gray). Focal hyperpigmentation frequently follows drug-induced lichen planus (also known as lichenoid drug reactions). Morphological patterns of pigmentation secondary to drugs or heavy metals are shown in **Table 2**.

Treatment

The most important factor in the management of drug-induced or heavy metal dyspigmentation involves the identification and discontinuation of the offending drug or heavy metal. Most mucocutaneous pigmentation is reversible and spontaneously resolves with avoidance of the inciting drug. In addition, exposure to sun or UV light may increase pigmentation, especially after sensitization with a photosensitizing medication. Sunscreen use and vigilant avoidance of the sun are helpful to prevent progression or recurrence of pigmentary changes.

Finally, topical depigmenting agents and laser treatments (eg, Q-switched alexandrite laser, Q-switched ruby laser) have been reported to improve cases of permanent dyspigmentation.

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