

How to Treat

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Overview of pigmentary disorders

DISORDERS of pigmentation are a common presentation in dermatology and general practice. The aesthetic appearance of either hyperpigmentation or hypopigmentation, especially in the visible parts of the skin, can have major psychosocial implications. Although it is more of a cosmetic problem, a disorder of pigmentation can occasionally be associated with an underlying systemic disorder. It is therefore important to recognise the causes of pigmentary disorders to achieve the best treatment outcome.

This article discusses pigmentary disorders in general including the underlying pathological mechanisms and management. It then looks at individual hyperpigmentary and hypopigmentary conditions in more detail.

The single most important substance determining human skin colour is the pigment melanin. Other compounds that may contribute to the skin colour include carotenoids and haemoglobin.

Melanin is produced by melanocytes during melanogenesis. This occurs within melanosomes, which are small membrane-bound packages. When melanosomes become full of melanin, they move along the arms of melanocytes and are transferred to the keratinocytes. One melanocyte supplies melanin to about 36 keratinocytes. People have the same number of melanocytes but their skin colour is determined by the amount and types of melanin the melanocytes produce. Melanocytes

Disorders of pigmentation — Part 1: Hyperpigmentation

This is the first of a two-part series on disorders of pigmentation. In Part 1, we discuss the nature of pigmentary disorders and then focus on hyperpigmentary disorders. In Part 2, we cover hypopigmentary disorders.

are found in the skin or epidermis, hair follicles, eye, nervous system, leptomeninges and the inner ear. Melanocytes in the skin and other body sites have a common embryological origin from the neural crest. They migrate from here into these different body sites.

The production of melanin is mainly regulated by the enzyme

tyrosinase. Melanocytes produce two types of melanin that give the skin its colour. The most common form of melanin is eumelanin, which gives a brown-black colour and is more abundant in people with dark skin. Pheomelanin gives a red-yellow colour to the skin. Both the amount and type of melanin produced is controlled by

several genes, such as the genes for the MSH cell surface receptor and the melanosomal P-protein. These genes can regulate the variability of the skin colour in humans by mainly regulating the level and activities of enzymes involved in the melanin biosynthesis, mostly the enzyme tyrosinase.

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How To Treat – Disorders of pigmentation — Part 1: Hyperpigmentation

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Pathogenesis

Disorders of pigmentation can be due to a variety of genetic and acquired causes. This is because there are many genes involved in the different stages of melanin production and transport abnormalities may arise from any of these stages. In piebaldism, for example, melanocyte migration from the neural crest is defective. Other abnormalities may occur in the formation of melanocytes and melanosomes, or during the secretion of melanosomes to keratinocytes. Certain pigmentary disorders such as Waardenburg syndrome may also be associated with visual and neurological defects, owing to the defects' common embryological origin and migration from the neural crest.

Acquired conditions of pigment loss can arise from melanocyte destruction. This may be due to an underlying autoimmune disorder such as vitiligo, or inflamma-

Condition	Features
Pityriasis versicolor	Yellowish-white or copper-orange fluorescence
Vitiligo	Bright areas with sharp borders, varying in location and extent
Tuberous sclerosis	Patches; characteristic ash-leaf shape
Hypomelanosis of Ito	Whorled or streaked patterns.
Erythrasma	Shows coral red fluorescence
Melasma	Pigments in the outer epidermal layer of the skin are accentuated while the colour of the deeper dermal pigments is decreased

tory disorders, or be secondary to chemicals or drugs. Increased pigmentation similarly can be induced by many factors such as UV radiation, drugs, inflammation and hormonal factors. Abnormalities in the other pigment compounds such as carotenoids and haemoglobin may also result in certain pigmentary disorders.

Diagnosis

Many pigmentary disorders can

be diagnosed clinically. A detailed history and examination is important and often gives clues to the underlying cause. A lesion presenting from birth may be a naevus or a genetic disorder. A family history of a similar disease also favours a genetic disorder. Diffuse types of pigmentary changes may be due to metabolic, hormonal or nutritional causes. A preceding rash or injury to the skin suggests post-inflammatory hyper- or hypopig-

mentation. A detailed drug history may help to determine if the hyperpigmentation is caused by a phototoxic or allergic reaction, or from fixed drug eruptions.

Dermatoscope and Wood's lamp

The dermatoscope and Wood's lamp can assist the clinician in diagnosing certain diseases. Table 1 shows clinical features that may be detected under a Wood's lamp in a variety of pigmentary disorders. Dermatoscopy is a very useful tool in differentiating a benign melanocytic naevus, pigmented seborrhoeic wart from a malignant melanoma. Histological diagnosis will be required in some cases.

General principles of management

While mostly benign, both hyperpigmented and hypopigmented lesions, such as vitiligo or facial melasma, can profoundly affect a patient's emotional and psychological wellbeing and self-esteem.

Formal counselling from a mental health professional may be helpful. Education about the disorder and treatment options should be fully provided so that the patients can form realistic expectations and participate in making important decisions about their medical care. Patient support groups are helpful. Cosmetic camouflage is an option in some patients, especially on visible parts of the body.

Minimising sun exposure

Patients who have depigmented or hypopigmented skin should minimise sun exposure and use a sunscreen that provides protection from both UVA and UVB light. Tanning makes the contrast between normal and depigmented skin more noticeable. Sunscreen helps prevent tanning and also helps protect from sunburn and long-term damage. Moreover, hyperpigmentary disorders such as melasma and freckles can deteriorate with sun exposure.

Patterns of hyperpigmentary disorders

DISORDERS of hyperpigmentation may be localised (ie, circumscribed) or diffuse (table

2). Certain conditions such as poikilodermatous disorders cause reticulate and mottled type of

pigmentation (figure 1). Because of their cosmetic significance, facial and periorbital pigmen-

tation need special attention. There is no set algorithm or specific way to approach a patient with a

hyperpigmented lesion. However, figure 2 will help the clinician in approaching a patient.



Figure 1: Poikiloderma in left anterior chest and upper arm in a patient with mycosis fungoides.

Pattern	Disorders
Circumscribed	Freckles, lentigines, melanocytic naevi, melasma, acanthosis nigricans, post-inflammatory, fixed drug eruption, café-au-lait macules, mastocytosis, pityriasis versicolor
Diffuse	Drug-related, endocrinopathies, haemochromatosis, HIV
Reticulate and mottled	Poikiloderma of Civatte, erythema ab igne, genetic reticulate pigmentary disorders, poikilodermatous disorders (eg, mycosis fungoides and dermatomyositis), confluent and reticulate papillomatosis, livedoid vasculopathy, graft-vs-host disease, post-kala azar dermal leishmaniasis, systemic sclerosis
Blaschkoid	Pigmentary mosaicism, incontinentia pigment

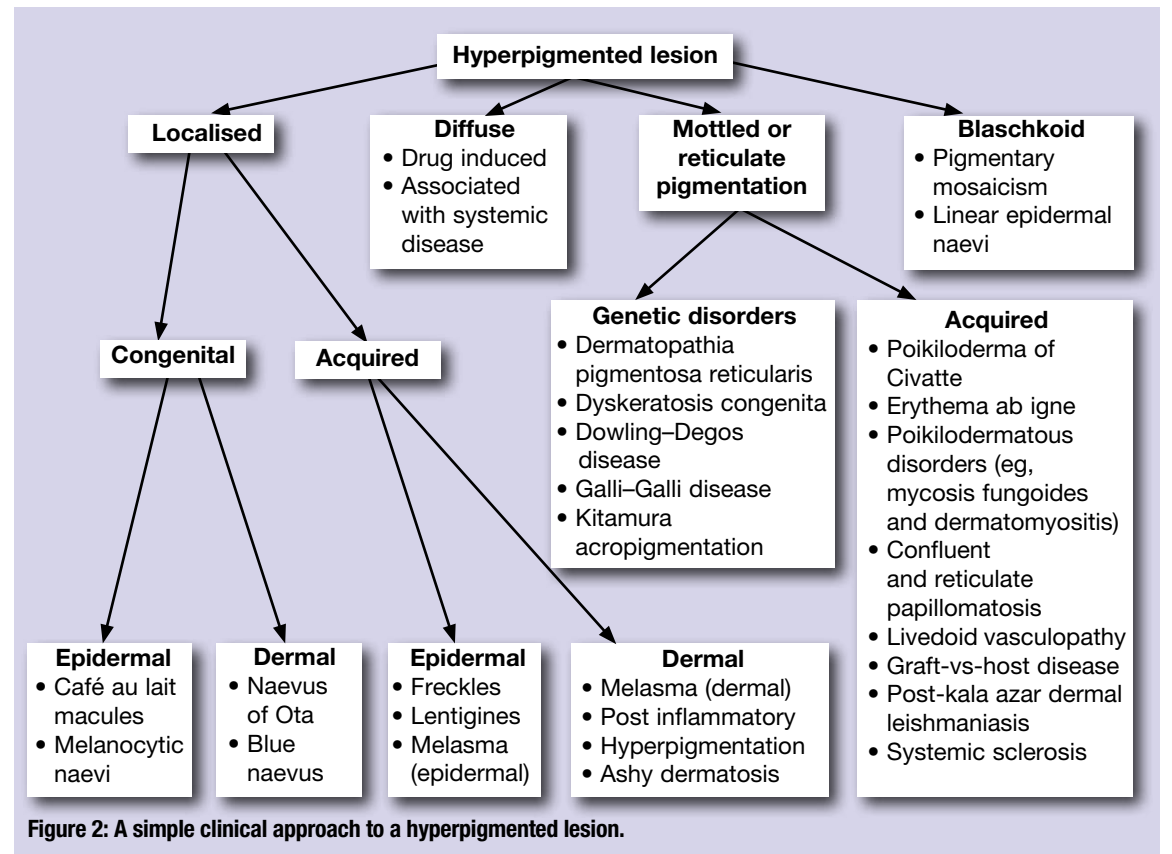


Figure 2: A simple clinical approach to a hyperpigmented lesion.

Circumscribed hyperpigmentary disorders

Freckles

FRECKLES are small flat brown circular spots arising on the face and other sun-exposed areas. They usually fade in winter with less sun exposure and as the keratinocytes are replaced with new cells. They are most often seen in fair skinned, red-haired people. Genetic tendency and sun exposure can predispose to development of freckles. Freckles represent an increase in the amount of melanin, not an increase in the total number of melanocytes. Increased tendency to develop freckles is seen in genetic disorders such as xeroderma pigmentosum. Axillary freckles are a feature in neurofibromatosis (table 3).

While freckles are a harmless

condition, some patients may be distressed by their appearance and seek treatment. Sun protection is essential in managing this condition if treatment is requested. There are several safe and effective methods that are available to help lighten or reduce the appearance of freckles. Treatment options include bleaching or fading creams (table 4), light application of liquid nitrogen, laser treatment and chemical peels. Frequently, multiple or a combination of treatments may be required for the best results. Preventive photoprotection starting in early childhood is important because freckles can easily recur with repeated UV exposure.

Lentigines

Lentigines are small, brown to black-coloured macular melanoses. They have several points of difference to freckles: there is an increased number of melanocytes in lentigines, lentigines are darker, persist throughout the year, and do not darken on exposure to sunlight. There are several types of lentigines, as listed in the box below. Multiple lentigines can occur in association with an underlying genodermatosis (table 3).

Café au lait macules

Café au lait spots are macules varying from light brown to dark brown with smooth or irregular borders. While having a few small

Table 3: Syndromes and genetic diseases associated with hyperpigmentation

Disorder	Associated Syndromes/Diseases
Freckles	Xeroderma pigmentosum Neurofibromatosis
Lentigines	Peutz-Jeghers syndrome Leopard syndrome Carney complex Xeroderma pigmentosum
Café au lait macules	Neurofibromatosis McCune-Albright syndrome Fanconi anaemia Tuberous sclerosis
Reticulate pigmentation	Dermatopathia pigmentosa reticularis Dyskeratosis congenita Dowling-Degos disease Galli-Galli disease Kitamura acropigmentation

lesions may be normal, a greater size and number can point towards an underlying genetic disorder. The most commonly associated systemic disorder is neurofibromatosis type 1 (figure 3). Other syndromes associated with café au lait spots are listed in table 3.

The café au lait macules themselves do not require medical care. Pigment laser (Q-switched Nd:YAG) offers clearance in about 50% of cases when cosmetic treatment is requested. Discussion about the possible post-treatment complications should occur prior to treatment. The complications include transient hyperpigmentation and hypopigmentation, slight scarring, permanent hyperpigmentation and recurrence.

Post-inflammatory hyperpigmentation

Post-inflammatory hyperpigmentation is a frequent complication following various cutaneous disorders. These cutaneous disorders may be infections (eg, tinea), dermatitis, drug reactions and inflammatory skin disorders (eg, lichen planus). Epidermal post-inflammatory hyperpigmentation appears light-brown to black whereas deeper dermal pigmentation has a grey to bluish appearance.

A variety of topical agents have been used to treat epidermal post-inflammatory hyperpigmentation, with varying degrees of success. These agents include hydroquinone, tretinoin cream, corticosteroids, glycolic acid (GA) and azelaic acid (table 4). A combination of topical creams and gels, chemical peels and sunscreens may be necessary and is only effective for epidermal hyperpigmentation. Laser treatment may be able to address dermal pigment deposition. Broad-spectrum sunscreens should be combined with any treatment regimen.

Melasma

Melasma presents as bilateral symmetric hyperpigmented macules commonly in the cheeks, the upper lip, the chin and the forehead (figure 4). The most significant cause of melasma is exposure to sunlight. Female hormones also play a role and appearance of melasma can be associated with pregnancy and contraceptive pills. There is a known genetic predisposition to melasma.

Melasma can be epidermal, dermal or mixed. Epidermal melasma has well-defined borders and is dark brown in colour. Dermal melasma is the common type with ill-defined borders and is bluish in colour. The mixed type has a combination of clinical features (see table 5).

Melasma can be difficult to treat and can be recurrent. There are several treatment modalities; these should always be combined with adequate sun protection. As shown in table 5, epidermal melasma has a good response to treatment while dermal melasma has a poor response.

Topical hydroquinone 2-4% cream twice a day with a sunscreen remains the first-line treatment. There are several other topical medications used in melasma that are listed in table 4. A combination of topical treatments ('Triple Combination Cream') with hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01% has been

Name and preparation	Clinical considerations	Mechanism of action	Side effects
Hydroquinone 2% and 4% preparations	Gold standard Most commonly used Apply twice daily in the affected area Should discontinue if no response after eight weeks	Most effective inhibitors of melanogenesis acts by inhibiting tyrosinase*	Irritation Phototoxic reactions with secondary post-inflammatory hyperpigmentation Irreversible exogenous ochronosis
Tretinoin 0.025-0.1%	Contraindicated in pregnancy Should apply only in the night Takes more than 12 weeks to see a response	Acts by increasing keratinocyte turnover and thus limiting the transfer of melanosomes to keratinocytes	Skin irritation Photosensitivity Paradoxical hyperpigmentation Burning, stinging, erythema, dryness and scaling Retinoid dermatitis leads to hyperpigmentation
Azelaic acid 20% cream	Superior to 2% hydroquinone Will not lighten skin with normally functioning melanocytes Apply twice daily	Weak competitive inhibitor of tyrosinase in vitro* Has an antiproliferative and cytotoxic effect on melanocytes Seems to target only hyperactive melanocytes (thus will not lighten skin with normally functioning melanocytes)	Skin irritation No phototoxic or photoallergic reactions have been reported
Kojic acid — in concentrations of 1-4%		A fungal metabolic product that inhibits the catecholase activity of tyrosinase*	Irritant contact dermatitis
Ascorbic acid 10-15% serum or cream	Twice daily application Takes 8-12 weeks to see a response	Has antioxidant properties and reduces melanogenesis	
Niacinamide		Suppresses the transfer of melanosomes to the epidermal keratinocytes	
Soy		Acts by reducing melanin transfer from melanocytes to keratinocytes	
Arbutin		Inhibits melanin synthesis by inhibition of tyrosinase activity*	
Paper mulberry		Inhibits melanin synthesis by inhibition of tyrosinase activity Isolated from a plant extract	
Liquorice extract		Inhibits tyrosinase activity of melanocytes without cytotoxicity	
Topical steroids	Monotherapy is not recommended Has synergistic effects with, and used for the reduction of irritation from, other products like tretinoin	Cause skin lightening as a result of reduced cell turnover and reducing production of melanocyte-stimulating hormone by reducing production of precursor steroid hormones	Skin atrophy with prolonged use
Hydroxy acids		Acts by epidermal remodelling and accelerated desquamation	Skin irritation

* Tyrosinase is the rate-limiting, essential enzyme in the biosynthesis of the skin pigment melanin; reduction of this enzyme leads to decreased production of melanin

Types of lentigines

Simple lentigines

- Very common condition
- Benign, isolated pigmented macules
- Seen in any part of the body including palms and soles
- Independent of UV exposure
- Usually do not need any treatment

Solar lentigines

- Small, discrete, irregularly shaped and uniformly brown macules
- Typically seen in sun-exposed areas together with other features of chronic sun damage

PUVA lentigines

- Relatively large macular pigmentation
- Develop as a complication of long-term PUVA (psoralen + UVA) therapy
- May be a marker of increased future development of melanoma and non-melanoma skin cancer

Ink spot lentigines

- Densely pigmented, relatively smaller macules
- Often alarm both the patient and the doctor because of their clinical resemblance to melanoma

shown to work faster.

Superficial chemical peels with glycolic acid, trichloroacetic acid (TCA), tretinoin or salicylic acid are being used to treat melasma in resistant cases. Three steps are involved in treating with chemical peels: careful patient selection, proper priming and post-procedural care (see box, next page).

Lasers that selectively target the hyperpigmentation in the correct depth can be used in resistant cases but with caution. Highly pigment-selective short pulsed Q-switched lasers that target the melanosomes are used in the treatment of both der-

mal and epidermal pigmentation. As they are selective of the target, there is minimal damage to the surrounding tissue. Repeated treatments are necessary to achieve a desirable outcome.

Fractional laser is a non-invasive treatment that uses a device to deliver a laser beam divided into thousands of microscopic treatment zones that target a fraction of the skin at a time. This laser treatment works at both the epidermal and dermal layers of the skin. Fractional lasers are FDA approved and have made lasers safer, especially for darker-skinned patients. Hyper-



Figure 3: Café au lait macules seen on the forehead of a patient with neurofibromatosis type 1. Note the neurofibroma on left of chin.



Figure 4: Melasma in a middle-aged woman, showing the classic bilateral hyperpigmented macules on the cheeks and other parts of the face.

pigmentation, hypopigmentation and scarring are potential complications. Patients with darker skin should be treated with caution as even slight inflammation may worsen the hyperpigmentation. Prior treatment with topical

bleaching creams and post-procedure sun protection is necessary to minimise complications. Oral tranexamic acid may be effective for some patients, but further studies are needed.

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How To Treat – Disorders of pigmentation — Part 1: Hyperpigmentation

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Ashy dermatosis (erythema dyschromicum perstans)

Erythema dyschromicum perstans, also called lichen planus pigmentosus, causes ashy discolouration of skin and is therefore also known as 'ashy dermatosis'. Ashy dermatosis is an asymptomatic eruption of oval, polycyclic, or irregularly shaped, grey-blue hyperpigmented macules on the trunk, the arms, the face, and the neck (figure 5). There are no systemic symptoms or associations. There are close similarities with lichen planus although the exact relationship is not clear. The disease is more common in Asian and Latin American people.

Different treatments have been tried but ashy dermatosis is usually resistant to treatment. Clofazimine has shown satisfactory results in some patients. Other treatments such as dapsone, potent steroids and bleaching creams have not shown satisfactory results.

Acanthosis nigricans

Acanthosis nigricans causes increased pigmentation with a soft velvety appearance on the sides of the neck, in the axillae and groin. There is also often an increased pigmentation of mucosal surfaces. The mechanism responsible for the pigmentation is unknown, but increased melanocytes-stimulating hormone activity is suspected. There are several types of acanthosis nigricans (see box, right).

The aim of treatment is to correct the underlying disease. This may involve multidisciplinary evaluation. Treatment of the lesions of acanthosis nigricans is for cosmetic reasons only. Topical medications that have been effective include keratolytics (eg, topical tretinoin 0.05%, ammonium lactate 12% cream, or a combination of the two) and triple-combination depigmenting cream (tretinoin 0.05%, hydroquinone 4%, fluocinolone acetonide 0.01%) nightly with daily sunscreen.

Erythrasma

Erythrasma is a chronic superficial infection of the intertriginous areas of the skin caused by *Corynebacterium minutissimum*. The typical appearance of erythrasma is well-

Table 5: Melasma categorised by depth of pigmentation and ease of treatment

Melasma type by depth of pigmentation	Description	Relative response to treatment
Epidermal	Well-defined borders Dark brown in colour Becomes prominent with Wood's lamp examination	Good
Dermal	Ill-defined borders Bluish in colour Become less obvious with the Wood's lamp examination	Poor
Mixed	Combined features	Partial



Figure 5: Ashy dermatosis on the face of a middle-aged woman.



Figure 6: Hyperpigmentation due to erythrasma in the right armpit.

demarcated, uniform, brown-red macular patches located over the inner thighs, crural region, scrotum and toe webs (figure 6).

The axillae, submammary area,

periumbilical region and intergluteal fold are less commonly involved in erythrasma.

Excessive sweating/hyperhidrosis, obesity, diabetes mellitus, warm climate and poor hygiene can predispose to the disease. Erythrasma can be confused with acanthosis nigricans (which has a velvety texture and ill defined borders), candidiasis (which shows more erythema and fissuring at skin creases and shows satellite papules around the lesion), psoriasis (which has more pinkish well-defined lesions), and tinea cruris (which shows an active scaly edge).

Wood's lamp examination of erythrasma lesions reveals coral-red fluorescence of lesions and is a helpful bedside test.

Oral erythromycin 250mg four times daily for two weeks is the treatment of choice. Topical fusidic acid or miconazole twice daily for 2-4 weeks are also helpful.

Three steps of a chemical peel

Step 1. Patient selection and counselling

1. Discussion with the patient should include:
 - The procedure and the expected outcome
 - Possibility of unexpected complications like increased pigmentation, hypopigmentation
 - That treatment needs to be maintained
2. Take care in approach to patients with unrealistic expectations, active skin infections (HSV), keloidal tendency, uncooperative or non-compliant patients (careless about sun protection or maintaining treatment)

Step 2. Skin preparation or priming (start 2-4 weeks before chemical peel)

1. Treat the pigmentation with 2-4% hydroquinone
2. Start a mild peeling agent like 0.025% retinoids, 6-12% glycolic acid
3. Start a sunscreen and avoid sun exposure
4. Stop the peeling agent three days before the peel

Step 3. Post-procedure care*

1. Maintain adequate sun protection
2. Do not pick, scrub or peel off the skin
3. Gentle wash and cleanse
4. Start the maintenance treatment when skin returns to normal

*Proper post-procedural care is mandatory in achieving good results and in preventing complications

Types of acanthosis nigricans

Obesity-associated acanthosis nigricans

- Most common type
- Also called pseudo-acanthosis nigricans
- May be a marker for higher insulin needs in obese women
- May be an early marker for metabolic syndrome in paediatric patients

Syndromic acanthosis nigricans

- HAIR-AN syndrome: hyperandrogenism (HA), insulin resistance (IR), and acanthosis nigricans (AN)
- Polycystic ovarian syndrome
- Uncontrolled diabetes mellitus
- Ovarian hyperandrogenism

Acral acanthosis nigricans

- Hyperkeratotic velvety lesions
- Found over the dorsal aspects of the hands and feet, with knuckle hyperpigmentation
- Seen in otherwise healthy African-American individuals

Drug-induced acanthosis nigricans

- Examples include nicotinic acid, systemic corticosteroids, oral contraceptives, fusidic acid

Malignant acanthosis nigricans

- Examples include gastric adenocarcinoma, Wilms tumour, osteogenic sarcoma
- May present as lesions that arise rapidly, are more extensive, and in atypical locations
- May be associated with tripe palms (thickened velvety palms that have the appearance of stomach lining of beef, pork or sheep)

Facial hyperpigmentation

FACIAL hyperpigmentation is one of the most common cosmetic complaints and requires special consideration. The presentation may be either diffuse or patchy. The causes may be multifactorial (see box, right), including genetic factors, sunlight, cosmetics and hormonal factors.

Periorbital hyperpigmentation

Dark circles around the eyes or periorbital hyperpigmentation can cause much psychological distress to the patient. Even though the condition is usually benign, it can be very resistant to treatment. It is a common condition and often familial. There are most likely multiple causative factors involved, including epidermal hypermelanosis, dermal melanosis, increased vasculature, and normal anatomic variants.

The vascular type can present with erythema predominantly involving

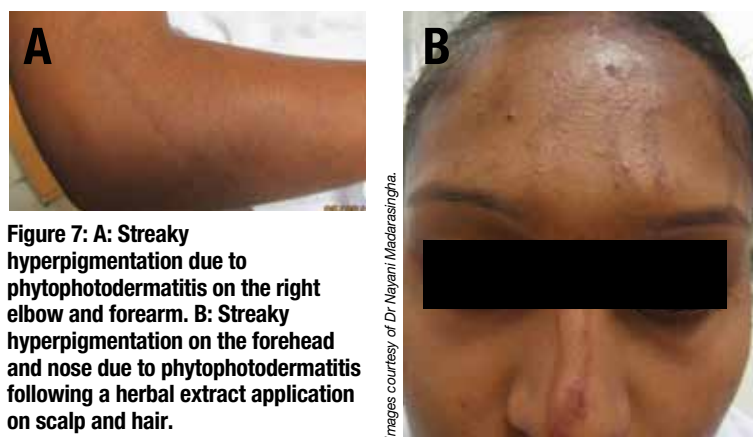


Figure 7: A: Streaky hyperpigmentation due to phytophotodermatitis on the right elbow and forearm. B: Streaky hyperpigmentation on the forehead and nose due to phytophotodermatitis following a herbal extract application on scalp and hair.

the inner aspect of the lower eyelids, with prominent capillaries or telangiectasia. Bluish discolouration of the lower eyelid can be seen as a result of visible blue veins. Constitutional type can present with a curved band of brownish to black hyperpigmentation with a velvety texture and often involving the upper eyelids (figure 8). Post-inflammatory

hyperpigmentation may be secondary to contact or atopic dermatitis. Shadow effects due to an overhanging tarsal muscle, eyebags or a deep tear trough can cause dark eye circles more commonly seen with ageing. Dry skin, hormonal disturbances, nutritional deficiencies and other chronic illnesses can also contribute.

Treatments that have been tried

Causes of facial hypermelanosis

Genetic

- Freckles
- Lentigines
- Naevus of Ota
- Pigmentary demarcation lines
- Xeroderma pigmentosum

Acquired

- Melasma
- Riehl's melanosis
- Poikiloderma of Civatte
- Berloque dermatitis
- Hori's naevus
- Actinic lichen planus
- Seborrhoeic melanosis
- Phytophotodermatitis (figure 7)
- Lentigo maligna

include skin-lightening creams, chemical peels, intense pulsed light, Q-switched ruby laser, autologous fat transplantation, combinations of fat grafting and blepharoplasty, and fillers. However, none have provided a satisfactory treatment.

Naevus of Ota

Naevus of Ota is a hamartoma of dermal melanocytes presenting as a blue or grey patch on the face, within the distribution of the ophthalmic and maxillary branches of the trigeminal nerve. The naevus can be unilateral or bilateral, and, in addition to skin, it may involve ocular and oral mucosal surfaces (figure 9).

Cosmetic camouflage makeup can minimise the disfiguring facial pigmentation. Other topical therapy is of no value. Pulsed Q-switched laser, Q-switched ruby, Q-switched alexandrite, and Q-switched Nd:YAG

lasers have shown good results.

Naevus of Ota can be associated with increased intraocular pressure and ophthalmic referral is necessary.

Hori's naevus

Hori's naevus is an acquired bilateral naevus of Ota-like multiple brown-grey to brown-blue macules, in the malar region of the face. It is differentiated from the naevus of Ota by the later age of onset and lack of conjunctival, mucosal and tympanic membrane involvement. Lasers are the most commonly used treatment for this condition and achieve good results.

Riehl's melanosis (melanodermatitis toxica)

Riehl's melanosis is caused by frequent and repeated contact with small amounts of sensitising allergens in cosmetics at a concentration that is too low to produce typical eczematous dermatitis. However, the repeated contact over time and repeated sun exposure causes cumulative allergic



Figure 8: Periorbital hyperpigmentation of the constitutional type showing curved bands of brownish to black hyperpigmentation with a velvety texture.

contact dermatitis that results in basal cell damage and pigment incontinence. Many cases are preceded by mild erythema, oedema and pruritus, followed by a diffuse-to-reticulated pattern of hyperpigmentation.

Photo-patch testing

Patch testing and photo-patch testing will help in making a diagnosis. A photo-patch test is similar to a skin patch test except that the allergens are applied on the skin in duplicate. One set is exposed to a small dose of ultraviolet radiation (UVA) to detect a photosensitiv-

ity reaction. Standard patch test series, cosmetic series, fragrance series, and patient's personal products can be used depending on the suspected allergens.

Other management measures

Complete avoidance of the suspected allergen is necessary, leading to a gradual improvement. Topical creams containing 2-4% hydroquinone twice daily for 4-8 weeks combined with tretinoin may hasten the resolution of the hyperpigmentation.

Poikiloderma of Civatte

Poikiloderma of Civatte is a reddish-



Figure 9: Naevus of Ota, seen here prominently on the right forehead and face and smaller on the left temporal area.

brown, reticulate pigmentation with atrophy of the skin and telangiectasia that occurs on the lateral cheeks and sides of the neck. It is seen more commonly in middle-aged women. Photosensitising chemicals in perfumes or cosmetics together with chronic sun exposure have been implicated in the pathogenesis of poikiloderma of Civatte. Hormonal changes related to menopause or low oestrogen levels may also be a causative factor.

There is no specific medical treatment for poikiloderma of Civatte. Educating the patient about

avoiding sun exposure and the proper use of sunscreens is most important.

Berloque dermatitis

Berloque dermatitis has drop-like or streak-like hyperpigmentation on the face or neck that arises from the application of perfumes and subsequently being exposed to the sun. The principal management is discontinuation of the offending substance and/or limiting the use the perfumes to covered areas. A short course of topical corticosteroids may help if there is inflammation and discomfort.

Diffuse or systemic causes of hyperpigmentation

DIFFUSE hyperpigmentation may be due to an underlying systemic disease (eg, Addison's disease, hyperthyroidism, haemochromatosis) or it may be a side effect of medication use.

Addison's disease

In Addison's disease, hyperpigmentation occurs over the entire body with accentuation in old scars and

in skin creases. The nail beds and the oral mucosa may also become hyperpigmented. The hyperpigmentation is caused by an increased activity of the melanocyte-stimulating hormone and adrenocorticotrophic hormone, both of which are capable of stimulating pigment production. Vitiligo, which is also an autoimmune disorder, can be associated in patients with Addi-

son's disease as part of a multiglandular deficiency syndrome.

Other systemic conditions

Hyperthyroidism causes a pattern of hyperpigmentation similar to that in Addison's disease, especially in patients with darker complexions. Haemochromatosis, a disorder of iron storage and deposition, can cause a slate-grey hyperpig-

mentation owing to the deposition of haemosiderin. In scleroderma, hyperpigmentation is generalised, but there is accentuation of the brown colour on the dorsal surface of the arms and hands. Occasionally, vitiligo-like hypopigmentation will be interspersed within areas of darkened skin.

Hyperpigmentation associated with malignancies is most classi-

cally found with carcinoma of the lung. The pigmentation occurs because of the melanocyte-stimulating hormone-like activity of polypeptides produced by such tumours. Generalised melanosis may also be seen with advanced, widespread melanoma, in which case the colour is due to the pigmented compounds produced directly by the malignant cells.

Reticulate and mottled hyperpigmentary disorders

RETICULATE pigmentary disorders cause net-like patterns of cutaneous hyperpigmentation that are seen in both congenital and acquired conditions (see tables 2 and 3). A formal diagnosis of any underlying disorder should be made because it may be treatable and/or associated with malignancies and systemic diseases.

Erythema ab igne

Erythema ab igne is characterised by localised areas of reticulate erythema and hyperpigmentation that result from chronic heat exposure (eg, heating pads, heating blanket, laptop computer). It is typically seen in middle-aged or elderly patients, and is more common in women.



Figure 10: Confluent and reticulate papillomatosis on the back showing red and verrucous papular lesions coalescing to form plaques.

There may be an initial erythema which then, with repeated exposure to heat, evolves into a non-blanching dusky hyperpigmentation with epidermal atrophy. Hyperkeratosis and bullae may be seen in the late stage. Squamous cell carcinoma may develop as a possible long-

term consequence.

Confluent and reticulate papillomatosis

The lesions of confluent and reticulate papillomatosis are red, verrucous, minimally scaly papules, which coalesce to form brown plaques (fig-

ure 10). It usually develops between the breasts and in the midline of the back, and gradually spreads over the breasts and abdomen. With progression, the lesions acquire the characteristic reticulate appearance. This condition is commonly seen in young females.

The treatment of choice for confluent and reticulate papillomatosis is minocycline 100-200mg per day for weeks to months. Other antibiotics that have been tried include clarithromycin, erythromycin and azithromycin. Isotretinoin, tacalcitol and calcipotriol are useful topical treatments.

Prurigo pigmentosa

Prurigo pigmentosa is a rare

inflammatory skin disease characterised by pruritic, erythematous urticarial papules that are symmetrically localised on the trunk. The lesions resolve, leaving reticulate pigmentation. Lesions in different stages are usually present together at any one time; the condition has a waxing and waning course. Several causative factors have been implicated such as ethnic predisposition, environmental causes, seasonal variation, mechanical stimuli and contact allergens. Different medications have been tried with variable results. Antihistamines and steroids have been found to be ineffective while minocycline, tetracycline and doxycycline have shown promising results.

Medication-induced hyperpigmentation

MANY drugs are known to cause diffuse or localised hyperpigmentation. These are summarised in table 6, see next page.

Drug-induced pigmentation

The following features point to a drug-induced pigmentation:

- The increased pigmentation starts gradually after initiation and fades when drug is discontinued.
- The hyperpigmentation shows photo-aggregation.
- Involvement of cartilage, mucosa, nail and scar.

Fixed drug eruptions

Fixed drug eruptions are common and have some unique features. They are typically of acute onset and appear as annular, oedematous, reddish-brown to violaceous macules or plaques. These erythematous patches or plaques gradually fade with residual hyperpigmentation. The centre of the patch may blister or become necrotic (figure 11). Their diagnostic hallmarks include residual hyperpigmentation and recurrence at previously affected



Figure 11: Fixed drug eruption manifesting as a blister with surrounding hyperpigmentation.

sites following re-exposure to the same drug. Local symptoms may include pruritus, burning, and pain. The initial eruption is frequently located on the lip or genitalia.

The common medications that may cause fixed drug eruptions are analgesics, muscle relaxants, sedatives, anticonvulsants and antibiotics. Patients should be counselled on medication avoidance and possible cross-reactions to similar medications.

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Table 6: Medications that cause hyperpigmentation

Drug	Description of hyperpigmentation
Antimalarials (eg, chloroquine, hydroxychloroquine, amodiaquine and quinacrine)	Bluish-grey or purple pigmentation in the pretibial areas
Chemotherapy agents (eg, bleomycin, 5-fluorouracil, adriamycin, hydroxyurea)	Bleomycin causes a pigmented banding of the patient's nails, generalised hypermelanosis to focal pigmentation of pressure points, linear or flagellated bands 5-Fluorouracil causes photosensitivity reaction in sun-exposed skin, followed by hyperpigmentation, hypermelanosis in the skin near infusion or portal irradiation sites Adriamycin causes pigmented patches in the oral mucosa and lateral aspect of the tongue Hydroxyurea causes nail bed and/or lunula hyperpigmentation and tongue pigmentation
Heavy metals (eg, silver, gold, iron)	Silver causes a generalised slate-grey pigmentation (argyria) that is most accentuated in sun-exposed areas and often involves a patient's nails, sclera and mucous membranes Gold causes a blue-grey hyperpigmentation of sun-exposed skin, known as chrysiasis Iron causes a permanent blue-grey discoloration
Tetracyclines	Tetracyclines cause a brown discoloration of the teeth in children Minocycline causes blue-black discoloration localised to scars, blue-grey pigmentation on the extremities, and a generalised 'muddy' brown hyperpigmentation in sun-exposed skin
Amiodarone	Blue-grey or violaceous pigmentation of sun-exposed skin and yellow-brown stippling of the cornea
Antiretrovirals — zidovudine	Reversible dyspigmentation of the nails, brown mucocutaneous hyperpigmentation
Clofazimine	Violet-brown or bluish cutaneous pigmentation most apparent in lesional skin (figure 12)
Psychotropic drugs	Slate or blue-grey pigmentation in sun-exposed areas of the skin



Figure 12: Violet-brown pigmentation in the face developing from clofazimine in a patient treated for leprosy.

Conclusion

PIGMENTATION disorders are usually considered to be cosmetic in nature. However, it is important to recognise that they can cause psychological distress to the patient. It is also important to remember that some hyperpigmentation disorders may be associated with an underlying systemic disease or be caused by a medication. A thorough history and clinical examination is required, and investigations or specialist referrals should be made where appropriate.



Online resources

eMedicine

www.emedicine.com/derm/

DermNet NZ

dermnetnz.org

Further reading

- Wolff K, et al. *Fitzpatrick's Dermatology in General Medicine*. 7th edn. McGraw-Hill Inc, New York, 2007.
- James WD, et al. *Andrews' Diseases of The Skin: Clinical Dermatology*. 11th edn, Elsevier Inc., Edinburgh, 2011.
- Burns T, et al. *Rook's Textbook of Dermatology*. 8th edn, Wiley-Blackwell, Hoboken NJ, 2010.



How to Treat Quiz

Disorders of pigmentation — Part 1: Hyperpigmentation— 11 April 2014

INSTRUCTIONS

Complete this quiz online and fill in the GP evaluation form to earn 2 CPD or PDP points.

We no longer accept quizzes by post or fax.

The mark required to obtain points is 80%. Please note that some questions have more than one correct answer.

GO ONLINE TO COMPLETE THE QUIZ

www.australiandoctor.com.au/education/how-to-treat

1. Which TWO statements are correct regarding the pathophysiology of pigmentary disorders?

- Melanin, carotenoids and haemoglobin all contribute to human skin colour
- Disorders affecting the enzyme tyrosinase may disrupt the production of melanin
- Melanocyte numbers are never affected in acquired conditions of pigment loss
- Darker skin colour is due to increasing numbers of melanocytes

2. Which THREE statements are correct regarding clinical features associated with pigmentary disorder under Wood's lamp examination?

- Pityriasis versicolor has a yellowish-white or copper-orange fluorescence
- Vitiligo has increased sharpness of borders
- Melasma has accentuated outer epidermal layer pigmentation
- Tuberous sclerosis has ovoid yellow patches

3. Which THREE statements are correct regarding the general management principles of pigmentary disorders?

- Formal counselling from a mental health professional may be helpful
- Management of patient expectations is important
- Tanning is a good strategy to improve

depigmented skin

- Sunscreen should be advised for both hyperpigmentary and hypopigmentary disorders

4. Which TWO statements are correct regarding the clinical features of circumscribed hyperpigmentary disorders?

- Melanocytic naevi, acanthosis nigricans and mastocytosis all have circumscribed hyperpigmented lesions
- Melasma presents as bilateral symmetric hyperpigmented macules
- Lentigines, unlike freckles, darken on exposure to sunlight
- Freckles in the axilla are a clinical feature of fibromyalgia

5. Which TWO statements are correct regarding the management of circumscribed hyperpigmentary disorders?

- Both epidermal and dermal melasma have a good, curative response to treatment
- 50% of café au lait macules may clear with pigment laser
- Maintenance therapy is not required after a successful chemical peel for melasma
- The primary aim of treatment of acanthosis nigricans is to correct the underlying disease

6. Which TWO statements are correct

regarding the clinical features and management of reticulate and mottled hyperpigmentary disorders?

- Confluent and reticulate papillomatosis usually forms between the breasts and on the back of young women
- Erythema ab igne is usually caused by prolonged cold exposure
- Squamous cell carcinoma may develop as a long-term consequence of erythema ab igne
- Prurigo pigmentosa may be effectively treated with antihistamines and steroids

7. Which TWO statements are correct regarding the clinical features of facial pigmentation?

- Periorbital hyperpigmentation is never familial nor due to contact dermatitis
- Naevus of Ota may be associated with increased intraocular pressure
- Riehl's melanosis results from frequent contact with sensitising allergens at a concentration that is too low to produce typical eczematous dermatitis
- Poikiloderma of Civatte is a drop-like or streak-like hyperpigmentation

8. Which TWO statements are correct regarding the management of facial pigmentation?

- Photo-patch testing helps the management of Riehl's melanosis by identifying the causative agent to avoid
- The principal treatment for Berloque dermatitis is discontinuation of the offending substance
- Periorbital hyperpigmentation is readily treated with a chemical peel
- Ophthalmology referral is essential for patients with Hori's naevus

9. Which TWO statements are correct regarding the clinical features of medication-induced hyperpigmentation?

- Drug-induced pigmentation usually fade when the drug is discontinued
- Drug-induced pigmentation usually occurs in areas not exposed to the sun
- Fixed drug eruptions are usually gradual in onset
- Common medications that may cause fixed drug eruptions include analgesics and antibiotics

10. Which THREE medical conditions may cause diffuse or systemic hyperpigmentation?

- Lung cancer
- Addison's disease
- Raynaud's disease
- Hyperthyroidism

CPD QUIZ UPDATE

The RACGP requires that a brief GP evaluation form be completed with every quiz to obtain category 2 CPD or PDP points for the 2014-16 triennium. You can complete this online along with the quiz at www.australiandoctor.com.au. Because this is a requirement, we are no longer able to accept the quiz by post or fax. However, we have included the quiz questions here for those who like to prepare the answers before completing the quiz online.

NEXT WEEK We conclude this series on disorders of pigmentation with a close examination of hypopigmentary disorders.