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The color of skin: brown diseases of the skin, nails, and mucosa

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Abstract Brown diseases comprise disorders leading to hyperpigmentation in skin and nails. Melasma is an acquired skin disorder that is characterized by brownish macules that typically occur on the face. Schamberg disease, also known as progressive pigmented purpura, is characterized by brown pigmentation with pepper spots on their edges. We summarize the epidemiology, pathogenesis, histologic features, and treatment choices for additional brown diseases, including melasma, pigmented purpuric dermatoses, postinflammatory hyperpigmentation, drug-induced hyperpigmentation, and pigmentations due to systemic or physiologic conditions.

Introduction

There are many skin disorders presenting with hyperpigmentation. Melasma, also known as chloasma, is a disorder typified by hyperpigmentation that usually occurs on the face. Schamberg disease (SD), which is also known as progressive pigmented purpuric disease, is exemplified by red-brown–pigmented patches with pepper spots on their borders. It is usually localized on the lower extremities. Other pigmented dermatoses include pigmented purpuric lichenoid dermatitis of Gougerot and Blum (PPLD), which is a recurrent, uncommon variant of pigmented purpuric dermatosis (PPD), a condition that usually affecting middle-aged men. Postinflammatory hyperpigmentation, drug-induced hyperpigmentation, Riehl melanosis, poikiloderma of Civatte, stasis dermatitis, seborrheic keratoses, and some systemic conditions present also as brown lesions in the skin.

Melasma

Melasma is a commonly acquired disorder of hyperpigmentation, occurring on the face. It affects millions of people worldwide with a higher prevalence in women and more evident in people with darker skin. It is triggered by sun exposure, but multiple etiologies have been implicated, such as hormones, genetics, and medications.[1,2]

The word melasma comes from the Greek word *melas,* which means black. Chloasma is also used in the medical

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literature, which originates from the Latin word *chloos* (meaning greenish). These terms refer to the brownish aspect of the pigmented lesion.[3]

Epidemiology

The prevalence of melasma in the general population is unclear. It varies between 1.5% and 33.3% depending on the ethnicity, gender, skin type, and geographic locations; however, melasma is not limited to men. It has a higher prevalence in pregnant women of 50% to 70% and is also more common in Asians, Hispanics, and Africans than in white people.[4,5]

Pathogenesis and etiology

The main pathology in melasma is the increased melanogenesis, which results in hyperpigmentation. There are three types of melasma: epidermal, dermal, and the mixed type. In studies, enlarged melanocytes and increased melanosomes have been seen in the epidermis. Pigment migration throughout the layers, particularly in the basal and upper part of the basal layer, is increased. In the dermal subtype, melanophages and lymphohistiocytic infiltrates with increased melanin deposition may be seen. Mixed melasma has both the characteristics of the epidermal and dermal types.[2] There is solar elastosis, an increase in the blood vessels combined with basement membrane disruption, and there is an higher number of mast cells in the dermis.

There is an increase in the vascular endothelial growth factor (VEGF).[4] The elevated VEGF in keratinocytes plays a significant role in the increased vascularization of the blood vessels, vessel size, and vessel density, which are greater in the melasma area. The vascularity is the outcome of the solar elastosis. Levels of a type of receptor tyrosine kinase and tumor marker called c-Kit are also elevated and represent a strong melanogenic cytokine associated with solar elastosis. Both cause epidermal melanogenesis, with solar elastosis representing an accumulation of degenerated elastic fibers in the dermis. Solar elastosis occurs in 93% of melasma. The stem cell factor (SCF) and its receptor c-Kit expressions are increased around the dermal fibroblasts in the pigmented dermis.[6]

Mast cells play a role in melasma by releasing histamine to stimulate the proliferation and migration of melanocytes via protein kinase A activation. With ultraviolet (UV) exposure, histamine release in the dermal mast cells is upregulated.[7]

The cause of these changes in the skin remains unknown, although there are many known triggering factors, including UV exposure, hormones, oral contraceptives, pregnancy, procedures, and genetic predisposition.[3]

UV light is both an initiating and exacerbating factor for melasma. Melasma usually worsens in the summer due to the increased exposure to UV radiation and the subsequent melanogenesis (the migration of melanocytes to the epidermis) and cytokine production improves in the winter. Interleukin-1 (IL-1), α–melanocyte-stimulating hormone (MSH), VEGF, and SCF are the cytokines that are led by UV and cause the upregulation of melanocyte proliferation and activity.[1–3] UV radiation can also release free radicals that stimulate the melanin production.[8]

Female sex hormones play a significant role in the development and aggravation of melasma, as demonstrated by the increased prevalence in pregnancy and with the use of oral contraceptives.[9] Curiously, oral contraceptives do not cause melasma initially but only after 1 to 3 years of ingestion. This type of hyperpigmentation is more resistant to treatment than pregnancy-related cases.[10]

Progesterone and estrogen receptor expression is higher in the dermis and epidermis of pigmented skin and stimulate melanogenesis,[2,8] with estrogen-inducing melanogenic enzymes such as tyrosinase, tyrosine-related protein 1, tyrosine-related protein 2, and melanocyte-inducing transcription factor. The progesterone effect in melasma is controversial. Some studies have reported that patients who are given estrogen alone do not develop melasma contrary to progesterone; however, the synthetic progestin levonorgestrel found in oral contraceptive is involved. There are other reports suggesting that the progesterone components in oral contraceptive pills may prevent melasma by reducing the proliferation of tyrosinase activity and the effects of estrogen.[8,9] One study found increased serum levels of the luteinizing hormone, with no increase in the serum level of the follicle-stimulating hormone, adrenocorticotropic hormone, β-MSH, thyroid hormone, prolactin, and cortisol in patients with melasma.[1]

Genetic predisposition plays an important role in the development of melasma, with up to a 50% family history. Patients with darker skin (Fitzpatrick IV-V) are more prone, where in identical twins both will develop melasma.[2,8] There is also a higher frequency in men of Fitzpatrick IV to V. In one report, the ratio of family history of melasma was 70.4% for men with melasma. Another study, including 324 women with melasma, demonstrated a 48% incidence of melasma in relatives and patients with a family history of members with darker skin compared with patients with a negative family history.[11]

Thyroid disorders are also thought to be associated with melasma, as evidenced in a study that showed an increased frequency of thyroid disorders in patients with melasma being four times greater than in the control group.[11] Other studies found that thyroid diseases were not more frequent in these patients compared with the general population.[2] One report revealed that 6.4% of patients with melasma had hypothyroidism in association with reduced serum zinc levels.[12]

Clinical features

Melasma is characterized by symmetrical brownish macules with irregular contours that appear in sun-exposed areas.[3] There are three clinical patterns: centrofacial, malar, and the mandibular pattern. The centrofacial pattern is the most

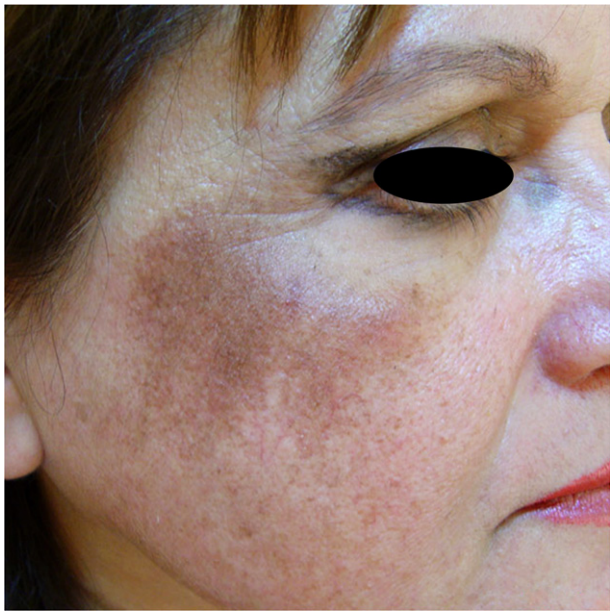

Fig. 1 Centrofacial melasma, brown macules with irregular contours.

common type, which is seen on the forehead, nose, cheeks, upper lip, and chin. Generally, melasma present with an overlap of these three clinical patterns (Figure 1). In the malar pattern, lesions are especially seen on the cheeks and nose. In the mandibular pattern, lesions are located on the ramus of the mandible.[1,13]

Some authors prefer a different classification such as: central, peripheral, mixed and extra facial. A study in Brazil reported the predominance of centrofacial melasma in Brazilian women followed by mixed type melasma.[14] Melasma may also be seen on the forearms, but rarely on the sternal region. A Wood lamp examination helps to determine the localization of the pigment (epidermis, dermis, or both), but it may not have any histopathologic support. In patients with darker skin, it is limited to detecting the dermal deposition.[13,14] If the lesion is enhanced with the Wood lamp it is epidermal; if it is not enhanced with the Wood lamp, then it is mostly dermal. In the mixed pattern, some areas of the lesion are enhanced and some are not with the Wood lamp examination. Recent studies have shown that dermal pigment deposition is more common, which may be unnoticed with the Wood lamp.[1]

The Melasma Area and Severity Index is used to both measure the clinical severity of facial melasma and evaluate the efficacy of the treatment. The involvement area, the darkness of the lesion, the localization (forehead, right malar, left malar, and chin) are assessed in the Melasma Area and Severity Index.[13]

The dermatoscopic findings of melasma include a dark brown, well-defined reticular network on a light-brown, pigmented area with a vascular component. If the pigment is located in the dermis, a bluish-gray color is seen.[5]

Melasma typically affects adult women in the reproductive age, but it also occurs in men with Fitzpatrick skin type IV to VI. The melasma onset is in the second to fourth decade and its duration can extend to as much as 10 years. In men, the malar pattern is more common than the centrofacial pattern.[4,14]

If we compare men and women with melasma, hormonal factors, such as pregnancy, oral contraceptive drugs, and hormonal therapy are considered to be the most common triggering factors in women. As the role of estrogen is known in the induction of pigmentation, estrogen, and testosterone, an imbalance might play a role in the development of melasma in men. Tadokoro et al showed that testosterone decreases the melanogenesis by reducing the level of intracellular cyclic adenosine monophosphate and inhibiting the tyrosinase. In some studies, a decreased level of serum testosterones in men with melasma were reported, and these findings were thought to be associated with the subtle testicular resistance.[5] One investigation[15] reported that melasma in men can occur as adverse effect of finasteride used for androgenetic alopecia. It is a hypothesis that by increasing testosterone serum levels and aromatization of testosterone to estradiol, melasma pigmentation might be induced.[15]

The diagnosis of melasma is generally conducted clinically. The differential diagnosis includes postinflammatory pigmentation, solar lentigo, freckles, lichen planus pigmentosus, discoid lupus erythematosus, pigmented contact dermatitis, erythema dischromicum perstans, drug-induced pigmentation, Hori nevus, erythromelanosis follicularis faciei, and macular amyloidosis.[2,11] These diseases can also accompany melasma so an extensive investigation of medical history and an examination is the first rule before the treatment. A Wood lamp examination, and histopathologic findings, if necessary, can help the differential diagnosis.[11]

Treatment

The most important aspect regarding treatment of melasma is sun protection and the avoidance of other exacerbating factors. Patients should be advised to avoid UV light, to wear broad hats, and apply sunscreen creams with sun protection factor of at least 30.[13]

Table 1 Agents and their mechanisms[16–19]

Tyrosinase inhibitors: hydroquinone, azelaic acid, Kojic acid, ascorbic acid, arbutin, rucinol, resveratrol, N-acetyl glucosamine, licorice extract
Stimulation of keratinocyte turnover: retinoids
Reducing the melanosome transfer: retinoids, soybean trypsin inhibitor
Inhibition of reactive oxygen species: ascorbic acid
Inhibitor of melanosome maturation: arbutin
Plasmin inhibitor: tranexamic acid
Melanin removal: chemical peelings, lasers

The treatment of melasma includes topical preparations, chemical peels, and lasers. Oral medications and dietary supplements have also been used for the prevention of relapses, either alone or in combination with topical formulations. Melasma is a condition that is hard to treat and relapses may occur frequently when the therapy ends. Generally, combination therapies are chosen for the difficult cases. Many patients benefit from camouflage makeup; however, melasma is far more challenging for covering the hyperpigmented areas.[16]

The principles of therapy should be the inactivation of the melanocytes, inhibiting the synthesis of melanin, and the disruption of the accumulated melanin. Avoidance of exacerbating factors such as UV light, pregnancy, oral contraceptive drugs, hormonal therapies, and scented cosmetic, may help to inhibit the activity of melanocytes (Table 1).

Topical tyrosinase inhibitors

Tyrosinase is the enzyme that converts L-tyrosinase into L-3,4-dihydroxyphenylalanine. Copper interacts with this enzyme's active site. Several agents affect this enzyme and result in decreasing melanization.[17]

Hydroquinone (HQ). HQ is a tyrosinase inhibitor that has been used for treating melasma for over 50 years. It inhibits the melanin synthesis pathway and also increases melanosome destruction and even blocks the DNA and RNA synthesis within the melanocytes by binding the enzyme or by interacting with the copper. HQ can be used alone or in formulation combined with other agents. The Kligman formula is the most well-known formulation, and is composed of HQ, retinoic acid, and topical corticosteroid.[16,17]

In comparative trials, HQ 4% was found to be superior to 5% ascorbic acid. Four percent HQ is reported to have better efficacy than Kojic acid (0.75%) and 4% niacinamide. One Cochrane review reported that azelaic acid (20%) showed better improvement than the HQ 2%, but had lower efficacy than the 4% HQ.[20]

The lightening effect of HQ is mostly apparent after 8 to 12 weeks. The main adverse effect of HQ is irritation and facial erythema. Generally, the irritation is caused by the agents added to the hydroquinone, such as tretinoin, glycolic acid, and sunscreens. Side effects such as ochronosis, or leukoderma were lower than expected. There was no report of ochronosis with 4% HQ on using it more than 3 months.[17,20]

Azelaic acid 20%. Azelaic acid is a reversible inhibitor of tyrosinase. This molecule inhibits the mitochondrial respiration and DNA synthesis of the melanocytes. It also decreases the free radical formation. It only targets the hyperactive, abnormal melanocytes. The change in the pigmentation is observed best with 3 months of use. A combination with alpha-hydroxy acid improves the effectiveness in the melasma treatment. A study reported that a combination of 20% azelaic acid and alpha-hydroxy acid (glycolic acid 15% or 20%) showed the same effectiveness in the reduction of the pigmentation as treatment with 4% HQ. It can also be combined with retinoids.[16,21] Irritation, pruritus, erythema, burning, and scaling are the most common side effects of azelaic acid. Acneiform eruptions, vitiligo, telangiectasia, and hypertrichosis have been reported in some cases with azelaic acid rarely.[22]

Kojic acid 2%. Kojic acid is a hydrophilic fungal product that inhibits tyrosinase by chelating copper at the enzyme's active site. This agent is combined with hydroquinone and glycolic acid for the melasma. Adverse effects include sensitization and irritation.[13,16,22]

Ascorbic acid (vitamin C). Vitamin C is an antioxidant that inhibits the melanogenesis by acting as a reducing agent in the oxidative steps of the melanin synthesis. It interacts with the copper in the tyrosinase active site. There are oral and topical forms of vitamin C. Its stability is a problem in the topical forms.[22]

In one study with 14 patients with melasma, vitamin C was compared with glycolic acid (70%) and found to have better efficacy.[164] Two studies suggested that it could increase the efficacy with the combination of other therapies such as 20% trichloroacetic acid (TCA) peel, and 1064-nm Q-switched neodymium-doped yttrium-aluminum-garnet (Nd:YAG) laser.[20]

Arbutin and deoxyarbutin. Arbutin (7%) is a derivative of HQ, which is found in the bearberry plant. It is an inhibitor of tyrosinase and melanosome maturation. Deoxyarbutin is a synthetic form that is a more potent inhibitor on tyrosinase than arbutin.[16,17]

Retinoids

Various topical retinoids have been used effectively in the treatment of melasma. Tretinoin more often, and adapalene, are the agents that are used for lightening. Due to the slow responses, generally they are used in combination with hydroquinone and corticosteroids to intensify the epidermal penetration and delivery of the HQ.[13,22] Retinoids help to improve the pigmentation by shedding the epidermis and increasing the keratinocyte turnover. They also block the pigment transfer to the keratinocytes.[22]

A randomized, vehicle-controlled study of 0.1% tretinoin, showed a significant improvement in patients that used tretinoin cream once at night for 40 weeks compared with the patients that used vehicle. It was shown that the efficacy started late after 24 weeks. In the histopathologic examination, it was seen that the epidermal pigment decreased 36% in the treated area, but with a 50% increase in the vehicle-treated area. Adapalene 0.1% was compared with 0.05% tretinoin in one study for 14 weeks and the effects of the two agents were found to be similar.[16]

The most common adverse effects of tretinoin are erythema, irritation, and paradoxic hyperpigmentation. Adapalene is less of an irritant agent and may be more tolerable for patients for long-term use.[16,23]

The triple therapy combination which contains hydroquinone (4%), tretinoin (0.05%) and fluocinolone acetonide (0.01%) (modified Kligman formula) was found to be effective in several studies. In a study compared with dual therapy, 77% clearance with triple therapy combination were reported versus 47% clearance with dual therapy.[13] Fluocinolone

acetonide is not recommended for extended use in the facial area due to potential adverse effects.

Tranexamic acid

Tranexamic acid (TA) is a synthetic lysine analog that has been used for antifibrinolytic effects for years. Studies showed that tranexamic acid has the antiplasmin activity and inhibits the melanin synthesis by decreasing the α-MSH and interfering with the catalytic reaction of tyrosinase.[4,22] TA can be used topically and orally for the melasma treatment. It is used in a dose of 250 mg per oral twice daily. TA may also be combined with topical hydroquinone or triple combination cream. To reduce the risk of postinflammatory hyperpigmentation, TA is used with the laser application.[24]

The soybean trypsin inhibitor inhibits the transfer of the melanosome to the keratinocytes. Genistein and daidzein are the primary active metabolites of soy that have an antioxidant effect.[16,22]

Topical corticosteroids should be used as a combination therapy mostly in the triple-agent creams. They directly affect the melanin synthesis and inhibit the prostaglandin or cytokine synthesis in epidermis.[22]

Indomethacin (5%) acts similar to corticosteroids. It is effective in the vermillion area in the epidermal melasma.[17]

Chemical peels

Chemical peels have been used in combination with topical agents for many years in patients with refractory melasma. It is more effective in the epidermal type melasma. The effects of it change due to its concentration, acid type, duration, and the patients' physical features. Alpha-hydroxy acids (lactic acid, glycolic acid), salicylic acid, and TCA are the most common peels used in melasma treatment. Less often other peels such as pyruvic acid, mandelic acid, phytic acid, and amino fruit acid peels have been used and have shown an improvement in melasma.[13]

Glycolic acid. Glycolic acid (GA) is the most commonly used peel with concentrations varying from 20% to 70%. It is very safe and efficient due to its small molecule weight. It penetrates the epidermis easily, but ineffective in the dermal type melasma. Its action depends on the duration on the face and can be neutralized so that it has minor complications and it is safe even in patients with darker skin. Mild erythema, burning, and superficial desquamation are the most common side effects of GA. When the concentration is high, postinflammatory hyperpigmentation might be seen in patients with darker skin.[25] In several studies, the GA peel combined with the topical therapy (hydroquinone 4%, azelaic acid 20% plus adapalene gel 0.1%,2 and modified Kligman formula) have reported better results than with the topical therapy especially with the 50% and higher concentration of the GA peel.[26]

Lactic acid. Lactic acid is another alpha-hydroxy acid that can be used in epidermal melasma treatment. It has similar activities to glycolic acid, but it has not been used as often as GA in melasma.[16]

Salicylic acid (SA). SA is a beta-hydroxy acid that has an anti-inflammatory and diffuse whitening effect. A postinflammatory hyperpigmentation risk is low with this peel because its quick penetration into the skin.[22] SA peels can be used in all skin types (Fitzpatrick I-VI) in concentrations of 20% to 30%. The SA and mandelic acid peel combination had better efficacy and fewer side effects than in GA in several studies. Mild burning was the most common side effect, which disappeared after one or 2 days.[26]

TCA peels. It is effective in melasma, but it should be used carefully in patients with darker skin. Concentrations of 10% to 50% of TCA are available, but with higher concentrations, the risk of postpeel postinflammatory pigmentation and scarring increase. There is no need to neutralize the TCA peel, it can be controlled by the degree of skin frosting. The result of the TCA peel depends on the number of layers that are applied to the skin. TCA can be combined with a Jessner solution, topical vitamin C, and laser therapy such as Q-switched alexandrite laser or pulsed dye laser.[27] In a study with 100 recalcitrant melasma patients, the results of 55% to 75% GA and 10% to 15% TCA were compared. It was reported that TCA response was rapid with better results, but relapses were more common in the TCA group than in the GA group.[26]

Jessner solution. Jessner solution is a superficial peeling that includes resorcinol, SA, and lactic acid in the ethanol. Modified Jessner solution has lactic acid 17%, SA 17%, and citric acid 8% in ethanol 95% with the lack of resorcinol to prevent the allergic reactions.[22,28] In a study that compared the therapeutic effect of combined 15% TCA and modified Jessner solution with 15% TCA alone on melasma found the combination treatment much more effective and safe.[28]

Laser and light therapies

Lasers target various chromophores in the skin by using thermal energy. Lasers have been used more often in melasma treatment recently. Lasers and light-based therapies should be used carefully in Fitzpatrick skin types IV to VI and are preferred if the other therapies are ineffective.[22]

Intense pulsed light (IPL). IPL is a broad spectrum light (500-1200 nm) that can be used in melasma with a lower side effect profile. The IPL targets the pigmentation in the deeper layers and the vascularization, so it can be a good option for treating dermal and mixed type melasma.[29] Wang et al compared IPL (four sessions/once in a month) combined with 4% HQ cream and HQ cream alone. The IPL group showed a 40% improvement versus a 12% improvement in the HQ group.[13]

Q-switched lasers. Q-switched Nd:YAG and Q-switched ruby laser cause the melanosomes rupture and subcellular damage in the dermal vascular plexus. Due to the rebound hyperpigmentation effect of these lasers, it is not recommended in melasma treatment.[13] The low-fluence Q-switched Nd:YAG laser utilizes the 1064-nm wavelength, which targets the dermal melanosomes and does not harm the epidermis. The low-fluence treatment can be used on patients with darker skin with a lower postinflammatory hyperpigmentation (PIH)

risk.[22] Wattanakrai et al compared low-fluence Q-switched Nd:YAG laser treatment and topical 2% HQ with 2% HQ alone in a split-face randomized study in 2010.[22] Patients who have dermal or mixed melasma with the Fitzpatrick skin types III to V were included. According to the results, the laser-treated side of the face improved 92.5% versus 19.7% improvement on the HQ-treated side alone.[30] A drawback of laser treatment alone is the frequent recurrence.

Fractional lasers. Fractional lasers were introduced in 2004 and approved by the US Food and Drug Administration for melasma treatment. This modality induces microthermal damage in particular areas; treated and nontreated areas are together so that the healing is better and more rapid. With this laser, complications such as hyperpigmentation and scarring are seen less commonly. Fractional lasers are categorized into two group: nonablative fractional laser (NAFL) and ablative fractional laser.[30]

Nonablative fractional laser wavelengths are 1440 nm, 1540 nm, 1550 nm, and 1927mm. NAFL devices cause coagulative damage in the dermis by targeting the water-containing tissues. The surface of the epidermis stays intact, so there is no visible wound in the treated area, only erythema and edema may occur that lasts for 1 week. Studies have shown the efficacy of the NAFL in the treatment of recalcitrant melasma. It was compared with GA peel or triple cream therapy, both results with lasers were equal to other treatments or better than some of them in the early posttreatment phase.[22,30]

Ablative fractional lasers such as carbon dioxide lasers and erbium:YAG lasers have been used for the treatment of melasma. They show their effect by targeting water and independent melanin. Due to the fractioned approach, epidermal injury is less, the healing is fast, and the PIH is low.[2,30]

Picosecond lasers. Picosecond lasers have a shorter laser pulse that produces a high peak power and thus, results in pigment fragmentation with the photomechanical effect. The small particles are carried away more easily by macrophages, and less heat damage is seen in the surrounding area.[30,31]

In a randomized, split-face, controlled trial, two treatments with combined 7-week 2% HQ cream and 5-week picosecond laser (weekly) versus 7-week 2% HQ cream alone were compared and the picosecond laser and the 2% HQ treatment was found to have superior efficacy.[31]

Pigmented purpuric dermatoses

PPDs are chronic recurrent disorders characterized by petechiae, purpura, and sometimes telangiectasia with brown or yellow colors localized especially on the lower extremities (Figure 2). Sometimes lesions occur on the trunk or on the upper extremities. PPDs are not correlated with venous insufficiency and hematologic diseases, and the etiology is uncertain because there are few studies on PPDs in the literature.[32,33] The other names are described as persistent pigmented dermatoses, purpura simplex, and purpura pigmentosa chronica. PPDs include five major groups, which show different clinical, but similar histopathologic findings. These are Majocchi disease (purpura annularis telangiectodes) (1896), SD (1901), pigmented purpuric lichenoid dermatosis of Gougerot and Blum (1925), eczematoidlike purpura of Doucas and Kapetanakis (1953), and lichen aureus (Calnan, 1960).[34] Frequencies of these forms are as follows: SD forms more than half of all PPD, eczematoid-like purpura of Doucas and Kapetanakis 10%, lichen aureus 10%, Majocchi disease 5%, and pigmented purpuric lichenoid dermatosis 5%.[35] Some rare forms were also defined, such as a transitory variant,[36] and a linear variant.[37] The last one was the granulomatous variant of PPD.[38]

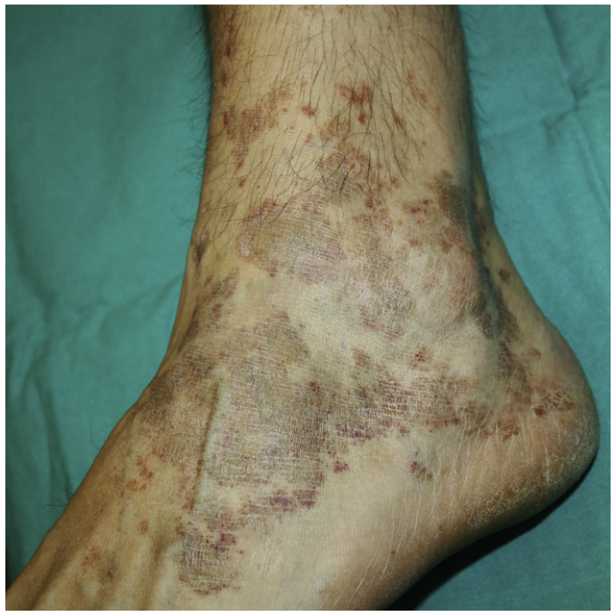

Fig. 2 Schamberg disease, erythematous and brownish macules with purpuric lesions on lower limbs.

Schamberg disease

SD was first reported by Jay Frank Schamberg (1870-1934) in 1901, and it takes his name. It is characterized by persistent golden-brown pigmentation with aggregation of pinhead-sized petechiae looking like a cayenne pepper. There is an additional SD, grain-itch dermatitis, both described by the Philadelphia dermatologist Jay Frank Schamberg.[39,40] Progressive pigmented purpuric disease is a synonym for SD.

Epidemiology

It is more common in men than women and uncommon in pediatric patients. Some pediatric cases have been defined in the literature,[41] but only one infant was reported.[42] Generally, it is localized bilaterally in the lower extremities; however, in some studies, it was reported to be unilateral SD.[43] Familial variants of SD have also been described.[44,45]

Pathogenesis and etiology

Histologically, the PPD showed five different pathologic patterns. Those patterns were spongiotic, interface, lichenoid, perivascular, and granulomatous.[46] The most common pathologic pattern was lichenoid (42.1%) followed by perivascular (37.4%), interface (10.3%), spongiotic (6.5%), and granulomatous (3.7%).[46] The most recognized pattern in SD was found to be the perivascular pattern. It showed fewer epidermal changes (hyperkeratosis, parakeratosis, or acanthosis), perivascular lymphocytic infiltration, red blood cell extravasation, hemosiderin deposition, endothelial cell swelling, spongiosis, lymphocyte exocytosis, and lichenoid lymphocytic infiltration.[32,46] The cause of SD is unknown; however, cell-mediated immunity may play a role in causing SD.[50] The vascular damage and erythrocyte leakage are secondary to a localized T cell–mediated reaction in the vicinity of the dermal capillaries. The etiology is unclear. Drug-induced SD cases are reported in the literature. Aspirin, carbromals, and thiamine have been associated with the disease.[51] Acetaminophen[52] and amlodipine[53] were reported to lead to SD. There has been one reported case showing that widespread PPD lesions were not only induced, but also rapidly provoked by dietary factors, namely cola and apple-cherry fruit spritzer.[54] The other factors causing SD are venous hypertension, stasis, exercise, trauma, contact allergy, and focal infections.[32] Hepatitis B antigenemia was also reported as causing SD.[55] Recently, SD has been described as being associated with chronic alcohol drinking.[56] And the underlying internal disease may be mycosis fungoides reported in the literature. PPD may occasionally evolve into cutaneous T-cell lymphoma. The coexistence of these two conditions has been reported, but is extremely rare.[57]

Clinical features

SD presents with discrete, red-brown purpuric patches on the legs. Nonpalpable pinpoint petechiae are seen which are referred as grains of cayenne pepper by Schamberg. The lesions mainly involved the lower extremities bilaterally but the thighs and buttocks may also be involved. Less commonly, lesions can occur on the upper extremity or become generalized.[39,40] Some rare or unusual manifestations have been described. Oral SD was detected both clinically and pathologically in 1965.[47] Other unusual localizations were reported in the genitalia[48] and in the plantar area of others.[49] SD is generally asymptomatic, sometimes mild pruritus accompanies.[39]

Treatment

Treatment options are limited. Pentoxifylline, colchicine, ascorbic acid, griseofulvin, topical steroids, and topical pimecrolimus were used as treatments for PPD.[32] One study in 2009 showed that aminapthone is satisfactory in controlling the SD progress[58] as aminapthone was used to treat patients with changes in capillary permeability and fragility. Psoralen and UV-A (PUVA) treatment[59] and narrow-band UV-B treatment[60] are mainly used to treat widespread lesions. Furthermore, topical photodynamic therapy, advanced fluorescence technology, pulse dye laser, and the last study using the 1540-nm erbium glass laser on SD lesions demonstrated that they might be safe and effective treatments for SD.[61]

PPLD of Gougerot and Blum

PPLD of Gougerot and Blum is an uncommon subtype of PPD. It was first described by Henri Gougerot (1881-1955) and Paul Blum (1878-1933).[62] PPLD is also known as Gougerot-Blum syndrome, PPLD of Gougerot and Blum, and purpura pigmentosa chronica. Gougerot-Blum disease is a skin condition that appears as multiple, small, brown papules that form plaques associated with purpuric lesions. These are usually observed in the legs, which then slowly spread to the rest of the body. Rare forms of the disease have been reported in the literature.[62,63]

Epidemiology

It is a rare form of PPD, and is generally seen in middle-aged men, but it can sometimes appear in young people also.[63] The frequency is 5% in pigmented purpuric dermatosis.[35]

Pathogenesis and etiology

The etiology is unclear. Infections, venous hypertension, exercise, some foods, some systemic diseases, and capillary fragility may aggravate PPD.[32,64,65] One case in the literature reported that diltiazem hydrochloride triggered PPLD.[66] The pathogenesis of these eruptions is unknown. One study about pathogenesis of PPD showed that all the lesions of PPD included predominantly T-cell infiltrate. B cells were rare. Macrophages did not comprise a significant component of the infiltrate.[67] Their findings would suggest that the primary process is more likely to be a cell-mediated immune event, driven by a skin specific subset of T helper cells, and that immune complex deposition within the papillary dermal vessels was the result of the immune complex causing secondary vascular damage. Histologically there are a lymphocytic lichenoid and bandlike infiltrate in the lesions.[46,68] Perivascular lichenoid infiltration of the lymphocytes is seen together with the macrophages, centered on the superficial small blood vessels of the skin with endothelial cell swelling and narrowing of lumina.[63] In 2015, one study[69] showed the histopathologic properties of PPLD. The most important histopathologic finding in PPLD is lichenoid lymphocytic infiltration (100%) followed by erythrocyte extravasation, endothelial swelling, interface change, and basal hyperpigmentation (66.7%), and lymphocytic infiltration, hemosiderin deposition, and spongiosis (33.3%).

In the literature an association between PPD and mycosis fungoides (MF) has been reported.[70] Histologically, MF commonly features a bandlike CD4+ lymphocytic infiltration aligned along the dermoepidermal junction like PPLD. One case regarding PPLD reported PPLD to be with a heavy bandlike CD4-positive lymphocytic infiltrate and has clonal

rearrangements of the A-chain of the T-cell receptors. The monoclonal expansion of the T cells in combination with certain histologic features of the MF might support a biologic relationship between PPLD and MF.[68]

Clinical features

Clinically, PPLD is characterized by multiple, small, brown lichenoid papules that form plaques associated with purpuric lesion. PPLD has mostly predilection for the legs, and but it can also be seen rarely on the trunk and thighs. Among the types of PPD, lichen aureus resembles PPLD the most, both clinically and histologically.[63] One case of PPLD was unilateral and localized on the dorsum of one foot and was presumably Kaposi sarcoma. A biopsy confirmed the diagnosis of PPLD of Gougerot-Blum.[64] In the other case of PPLD lesions were localized in the oral cavity.[65]

Treatment

The treatment of PPLD is usually difficult. Potent topical steroids were found to be effective.[63] Pentoxifylline, griseofulvin, cyclosporine, oral rutoside and ascorbic acid have been reported to have success in the treatment of PPD.[66] In a trial of seven patients with Gougerot-Blum's disease, 7 to 20 PUVA treatments resulted in the disappearance of the lesions. The authors commented that UV radiation alters the distribution and function of lymphocytes and leads to a disappearance of epidermal Langerhans cells.[71] And the other study of PUVA treatment of PPLD showed a dramatic decrease in CD4+ and CD1a+ cells and a marked reduction in the adhesion molecule receptor expression in all cases. They preferred the PUVA for the treatment of PPLD.[72] Narrow-band UV-B treatment in one case of PPLD was found to be successful; the lesions were totally eradicated.[73]

Purpura annularis telangiectodes (Majocchi disease)

Purpura annularis telangiectodes (PAT) is a less common variant of PPD which is characterized by symmetrical red-brown telangiectatic macules or patches, progressing to annular lesions with central clearing and atrophy.[74] It was described by Domenico Majocchi (1849-1929).

Epidemiology

It is a rare form of PPD, and is mostly seen in third decade. PAT is more frequent in women than men.[74,75]

Pathogenesis and etiology

The etiologies of these conditions are not clear. Venous insufficiency, various drugs, contact allergy to clothing dyes and infections may play a role in the etiology of PAT.[40,75]

In the histology, a perivascular lymphocytic infiltrate around dilated venules of the superficial dermal vascular plexus and erythrocyte extravasation are found. These findings are consistent with PPD.[74]

Clinical features

The lesions present on the lower limbs, rarely trunk and upper extremities may be involved. Clinically nonpalpable red-brown, occasionally pruritic patches progress to hyperpigmented halos. The lesions are usually symmetrically distributed on the legs and are occasionally symptomatic. PAT usually lasts several months with relapses and remissions.

Treatment

Most forms of PPD do not require treatment. Compression stockings and leg elevation may help to reduce the edema and stasis. Topical steroids are used for their anti-inflammatory effects. Methotrexate and PUVA can also be considered in the treatment of PAT.[74]

Postinflammatory hyperpigmentation

PIH is a reactive hypermelanosis that occurs secondary to a cutaneous inflammatory process, trauma, or cosmetic procedures. Several inflammatory diseases can cause hyperpigmentation, hypopigmentation, or both. After the erythema of the primary skin disease dissolves, a hyperpigmented macule or patch may last. PIH is more common in patients with darker skin and may appear in all areas not necessarily in sun-exposed areas. Although PIH is easily diagnosed from the patient's history and the presence of prior inflammation, some of the dermatoses cause PIH without a noticeable inflammation.[22,76,77]

Epidemiology

PIH can occur both in men and women at any age. Patients with skin type Fitzpatrick IV to V are more prone to this type of hyperpigmentation. In a study of 1412 patients, dyschromias were found the second most common diagnosis in African-American people, whereas this diagnosis was not included among the top ten most common diagnoses in white patients.[76,77]

Pathogenesis and etiology

PIH results from the abnormal production of melanin due to endogenous or exogenous inflammatory conditions. Prostaglandins, leukotrienes, cytokines, and reactive oxygen species that were released during the inflammatory condition all increase the melanogenesis.[78]

Several dermatoses lead to PIH, such as lichen planus, psoriasis, atopic dermatitis, polymorphous light eruption, erythema dyschromicum perstans, vesiculobullous diseases, drug eruptions, infections, and acne vulgaris. Exogenous causes of PIH include lasers, chemical peels, phototoxic reactions, and insect bites.[22,76] Laser resurfacing, laser hair removal, intense pulsed-light treatments, and other commonly

used laser and light therapies may cause PIH in patients with darker skin as an adverse effect of the therapy. Treating the patients with high-energy and high-density settings may increase the risk of PIH, treatment density appears to play a greater role in the development of PIH. Nonablative fractional lasers should be chosen for the patients who have the risk of PIH. By reducing the number of passes in one session, and extending the intervals between two sessions can reduce the incidence of PIH.[78]

In the histopathology of PIH, superficial dermal melanophages, including increased epidermal melanin, are seen. In epidermal type, there is an increased epidermal pigmentation due to the stimulation effect of cytokines and inflammatory mediators, epidermal growth factor, and reactive oxygen radicals. In dermal type, there is an increased pigmentation in upper dermis with degenerating keratinocytes and decreased pigmentation in epidermis. Dermal PIH also showed a significant dermal perivascular lymphocytic infiltration and higher expression of CD-68, c-Kit, and matrix metalloproteinase-2.[78,79]

Clinical features

PIH presents with hyperpigmented macules or patches in the distribution of the inflammatory prior disease. There are two clinical patterns of PIH. Epidermal hyperpigmentation tends to manifest with dark brown, asymmetrical and irregular macules (Figure 3). Dermal pigmentation appears as blue-gray or dark gray macules. Epidermal PIH can dissolve spontaneously within months with appropriate treatment. Dermal PIH may be resistant to therapies or dissolves in a very long time; however, repetitive inflammation may cause permanent dyschromia.[77] Sun exposure or the aggressive treatment modalities may worsen PIH.[77,78]

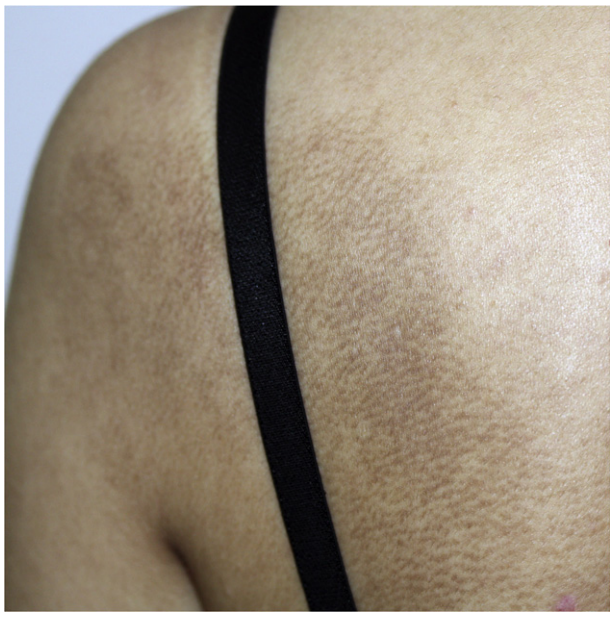

Fig. 3 Postinflammatory hyperpigmentation, dark brown, irregular macules on the back.

The diagnosis of PIH is based on a clinical examination with the history of previous inflammatory disease. Wood lamp can help to distinguish the epidermal and dermal pigmentation to predict the efficacy of treatments offered at the onset. The differential diagnosis of PIH includes melasma, acanthosis nigricans, Riehl melanosis, erythema dyschromicum perstans, the pigmentation of Addison disease, lichen planus, and tinea versicolor.[80]

Treatment

The treatment of PIH is the prevention and the treatment of the previous inflammatory disease. Protection from sun and using sunscreens are crucial. Treatment options are topical whitening agents, such as hydroquinone, retinoids, Kojic acid, and azelaic acid, chemical peels, and laser. The efficacy of the treatment depends on the pigmentation level. Epidermal PIH responds much better to treatment than dermal type.[81]

HQ is considered to be the gold standard of treatment for PIH and is often used as first-line therapy.

Combination of HQ with alpha-hydroxy acid, retinoids, corticosteroids, and ascorbic acid may improve the effect with decreased risk of irritation. In a study including 792 patients with PIH, the triple cream combination (hydroquinone 4%, tretinoin 0.05%, and fluocinolone 0.01%) compared with the dyad comparators (hydroquinone and fluocinolone; hydroquinone and tretinoin; and fluocinolone and tretinoin) and found to be more effective to whiten the skin after 8 weeks.[78]

Topical retinoids, including tretinoin, tazarotene, and adapalene, are commonly used for the treatment of PIH. However monotherapy is not recommended due to the irritation ad the risk of paradoxical hyperpigmentation. Combination of topical corticosteroid helps to control irritation, and improves epidermal penetration.[80]

Azelaic acid is one of the topical agents for PIH treatment. Combining azelaic acid cream 20% with GA 15% or 20% may improve the effect of the treatment.[78] GA and SA are the most common superficial peeling agents used for PIH. Peeling agents such as Jessner-TCA combination, TCA 35%, or phenol which have deep penetration, have the risk of causing more inflammation and worsen pigmentation. Lasers with longer wavelengths (1064-nm Q-switched Nd:YAG) are safer in treating patients with darker skin. They penetrate deeper but epidermis is also spared. Q-switched ruby 694-nm lasers can also be used due to their high reactivity on melanin. It is important to choose the appropriate skin type dosage to prevent permanent hypopigmentation.[81]

Drug-induced hyperpigmentation

Drug-induced hyperpigmentation is characterized by brownish pigmentation, mainly affecting the sun-exposed

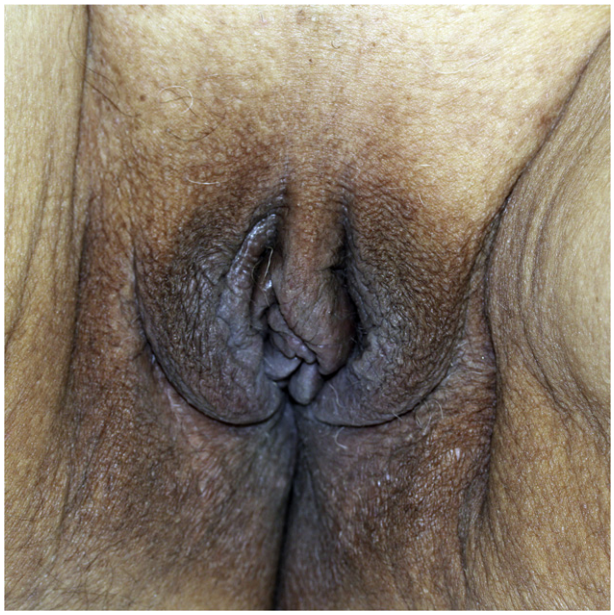

Fig. 4 Hydroxychloroquine induced dark brown macules and patches on the genital area.

areas and mucous membranes. Many drugs are accused of secondary pigmentation as an adverse effect, but the evidence is poor in this area especially for some drugs. Minocycline, tricyclic antidepressants, clofazimine, phenothiazine, antimalarial drugs, prostaglandin agonists, anticonvulsants, and sulfonylureas are the common drugs that cause pigmentation.[82,83] One of the most notable drug is clofazimine, which causes brown pigmentation in sun-exposed areas mimicking melasma. However, it becomes generalized and typically affects nails.[84]

HQ-induced hyperpigmentation presents with yellow-brown to gray-black macules and patches, which are seen mostly on the anterior side of the shins, forearms, face, and less commonly in the anogenital region.[85] They can also affect mucous membranes with patches on the hard palate (Figure 4).[86]

Psychotropic drugs such as phenothiazine, amitriptyline, chlorpromazine, desipramine, and imipramine, thioridazine, cause pigmentation in the sun-exposed areas by stimulating the secretion of the MSH. Oral contraceptives also darkens the nipples and areola, increases pigmentation of nevi, and aggravates the hyperpigmented patches of the face.[82]

There have been several reported cases of brown hyperpigmentation developing after the use of topical tacrolimus in other inflammatory disorders, including atopic dermatitis or lichen planus. This may be the result of increased SCF in keratinocytes treated with tacrolimus.[87]

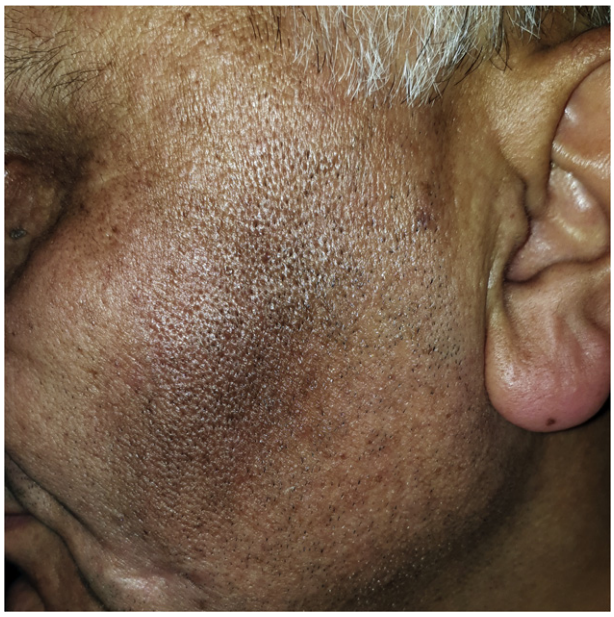

Fig. 5 Riehl melanosis, brown-gray diffuse pigmentation on the left cheek.

Riehl melanosis

Background

Riehl melanosis is a brown-gray reticular or diffuse pigmentation that occurs on the face and neck (Figure 5). It is a pigmented contact dermatitis caused by repeated contact with common cosmetics. Pruritus, scaling, and erythema precede the pigmentation.[84,88] During World War I, Gustav Riehl (1855-1943) identified patients with brown to gray facial pigmentation, mostly on the lateral aspects of the face and neck and primarily concentrated on the forehead, ears, temple, and zygomatic regions.[89,90] Later, Hoffmann and Habermann described a condition referred to as melanodermatitis toxica that was hypothesized to be a form of contact dermatitis associated with the use of certain oils and hydrocarbons. To date, the etiology of Riehl melanosis remains controversial, and although the majority of experts believe it is synonymous with pigmented contact dermatitis.

Etiopathogenesis

A variety of contact allergens, including textile, cosmetic, fragrance, and nickel have been implicated in pigmented contact dermatitis. Although the majority of cases occur due to direct contact with these allergens, a few cases secondary to contact with airborne allergens have been described.[91] The hyperpigmentation in pigmented contact dermatitis is caused by frequent and repeated contact with small amounts of sensitizing allergens. Allergens used in commercial products were too low in concentration to produce typical eczematous dermatitis, but rather accumulation of these allergens resulted in type IV cytolytic reaction.[92]

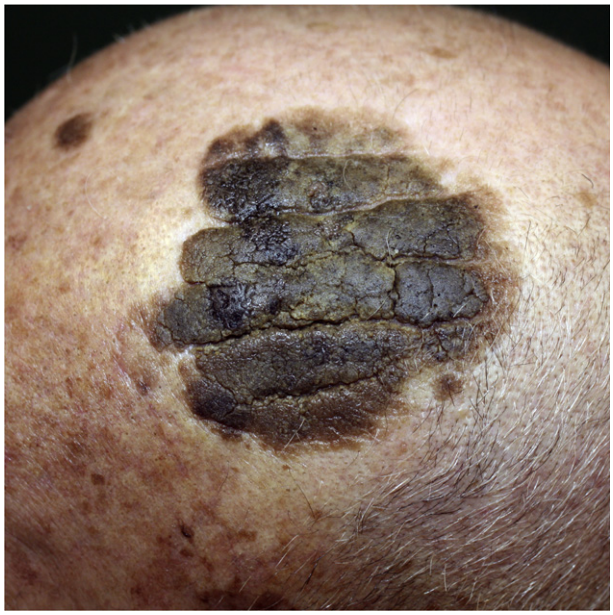

Fig. 6 Seborrheic keratosis, dark brown sharply demarcated plaque on the scalp.

Diagnosis

The diagnosis is based on clinical appearance. The history of cosmetic use should be questioned and if it is necessary, photopatch test may be helpful in the differential diagnosis. The differential diagnosis includes melasma, nevus of Hori, PIH, and phototoxic dermatitis.[84] In case of suspicion, a tissue biopsy can also be made. Histopathologic examination reveals basal cell vacuolization in the epidermis and there are superficial perivascular lymphocytic infiltrate and melanophages in the dermis.

Treatment

Complete avoidance of the suspected allergen is necessary. Treatment involves sun protection, skin whitening agents such as HQ, retinoids, and GA and other chemical peels. But the efficacy of these treatments is not satisfactory.[93] Other options include intense pulsed-light therapy, Q-switched Nd:YAG lasers, and other lasers with wavelengths that specifically target the hyperpigmentation.[94]

In addition, pilot studies have shown oral TA and compounded glycyrrhizin may also be of benefit.[93]

Seborrheic keratosis (SK)

SKs are benign, epidermal neoplasms that occur commonly in the older patients. The lesions are more common in the sun-exposed areas such as head, trunk, and extremities. SKs appearing more frequently after the third decade of life.[95,96]

Epidemiology

Despite the frequency of SK, little is known about the epidemiology of this disorder. The prevalence of SK increases by age. They usually develop after the age of 50, but they can also appear in young adulthood. One Australian study reported age-specific prevalence in 100 Australian adults. There was an increase in prevalence of seborrheic keratoses from 12% of 15- to 25-year-olds to 100% of those aged more than 50 years. There was no difference in prevalence between men and women.[97] One study investigated the prevalence of SK in people aged 15 to 30 years. There was an increase in prevalence with age from 15.7% in 15- to 19-year-olds to 32.3% in those aged 25 to 30 years.[98]

Pathogenesis and etiology

Although the pathogenesis is not completely understood, aging and cumulative UV exposure are independent risk factors for the development of SKs. Genetic factors are also important in the etiology of SK. Somatic activating mutations in *FGFR3* and *PIK3CA* oncogenes have been found in SK.[99,100] One study[101] investigated genetic alterations in SKs. The *FGFR3* gene mutations were the most frequent, detected in 12 of 25 (48%) SKs, followed by the *PIK3CA* gene (32%), *TERT* promoter (24%), and *DPH3* promoter mutations (24%). The role of human papillomavirus in the pathogenesis of SKs is unclear.[96] Investigations for the presence of human papillomavirus DNA in nongenital SKs have been reported.[102]

Histologically, well-demarcated proliferation of keratinocytes and small, keratin-filled cysts are seen in SK. A dermal lymphocytic infiltrate can be seen in irritated lesions. The histopathologic findings vary according to the subtypes of SK.[103] Six histologic variants of SKs have been described: acanthotic, hyperkeratotic, reticulated, clonal, irritated, and melanoacanthoma.[104,105]

Clinical features

SKs typically present as light or dark brown, sharply demarcated plaques, papules, or patches often with a keratotic surface. They are commonly found on the head (Figure 6), trunk, and extremities.[96] The size of SKs typically ranges from 0.5 cm to 1.5 cm. Diagnosis of SKs is generally based on clinical examination without the need for a biopsy. Dermatoscopy may be helpful in some cases[106] Comedolike openings, milia-like cysts, cracks, and ridges are characteristic dermatoscopic features of seborrheic keratoses.[107] The sudden appearance of multiple SKs referred to as the sign of Leser-Trélat, may be considered a paraneoplastic cutaneous marker of internal malignancy.[108]

Clinically, the differential diagnosis of SK includes verruca vulgaris, condyloma acuminata, solar lentigo, melanocytic nevus, acrochordon, acrokeratosis verruciformis, eccrine

poroma, Bowen disease, invasive squamous cell carcinoma, tumor of the follicular infundibulum, and melanoma.[96]

Treatment

Due to the benign character of SK, treatment is generally not required; however, lesions that are symptomatic or that cause cosmetic concerns can be removed. Cryotherapy is the most commonly used treatment. Curettage and excision may be used in larger lesions. Diode, 1064-nm Q-switched Nd: YAG laser, alexandrite, potassium titanyl phosphate, carbon dioxide laser, and electrodessication have been also used.[96,109,110] One study investigated safety and efficacy of hydrogen peroxide topical solution 40% in patients with SKs. A total of 937 patients, each with four index lesions, were treated with a single application of 40% hydrogen peroxide or placebo. At day 106, the proportion of patients for whom all four SKs were cleared was 4% in the active treatment group versus 0% in the placebo group.[111] Other treatment option, nitric-zinc complex have been recently reported.[50] SKs were treated with a novel aqueous solution containing nitric acid, zinc and copper salts, and organic acids (acetic, lactic, and oxalic acid). All patients with complete clearance showed no relapses at a 6-month follow-up.[112]

Poikiloderma of Civatte

Background

Poikiloderma refers to a skin condition consisting of telangiectasia, cutaneous atrophy, and macular hypopigmentation and hyperpigmentation (Figure 7).[113] Poikiloderma of Civatte was first described in 1923 by Achille Civatte (1877-1956) as the acquired poikiloderma of the face and neck. Poikiloderma of Civatte is a common skin disorder, mostly affecting the middle-aged or the elderly people who have lighter skin phototypes.[114]

Etiopathogenesis

The disease has a chronic, progressive, and irreversible course that continues with exposure to UV light. Although the exact pathogenesis of this condition is still unknown, several causative factors have been hypothesized, including long-term and chronic UV exposure, hormonal changes, and estrogen depletion associated with menopause, genetics, and photoallergic as well as allergic contact reactions to perfumes and cosmetics.[115,116]

Diagnosis

Pink-to-brown reticular patches with linear telangiectasia, mottled hyperpigmentation, and superficial atrophy form the clinical appearance of the poikiloderma of Civatte. It may involve the sides of the neck, the upper chest, and the peripheral face, sparing the anatomically shaded areas, such as submental region.[114,117] Riehl melanosis, erythromelanosis follicularis faciei et colli, poikiloderma atrophicans et vasculare, chronic graft-versus-host disease, and friction melanosis should be considered in the differential diagnosis.[95] In the differential diagnosis of Riehl melanosis and poikiloderma of Civatte, histopathology may help.

Clinically in Riehl melanosis, the skin atrophy is less intensive and telangiectasias are not present.[118,119]

The most prominent histopathologic feature, besides the classic poikilodermic changes, is solar elastosis of the papillary dermis. There are three different types of poikiloderma of Civatte: erythematous telangiectasia, pigmented, and mixed [120]

Treatment

No specific medical treatment exists for poikiloderma of Civatte. Patients should avoid the precipitating factors such as sun exposure, fragrances, and cosmetics. Patients should be instructed to minimize UV exposure and to apply a broadband sunscreen of sun protection factor 30 or more every day to all exposed areas of the face and neck. Pulsed dye laser and IPL have been used and found to be effective in the treatment of poikiloderma of Civatte.[121–123] Use of fractional photothermolysis, which creates microthermal injury zones in skin, to treat poikiloderma of Civatte has also been described.[124]

Stasis dermatitis

Stasis dermatitis is a common inflammatory dermatosis of the lower extremities occurring in patients with chronic venous insufficiency. It is associated with other chronic venous insufficiency findings such as varicose veins, brown hyperpigmentation, atrophie blanche (white scar tissue), lipodermatosclerosis, and leg ulcers.[125]

Epidemiology

Stasis dermatitis occurs more commonly in older age, with a prevalence 5.9% in a study in 68 patients with a mean age of 74 years.[126] In one study, stasis dermatitis was reported in 6.2% of patients over the age of 65.[127]

Etiology and pathogenesis

The development of venous hypertension leads to chronic venous insufficiency. The risk factors for chronic venous insufficiency include age, genetic factors, pregnancy, female sex, prolonged standing, obesity, and greater height. Venous

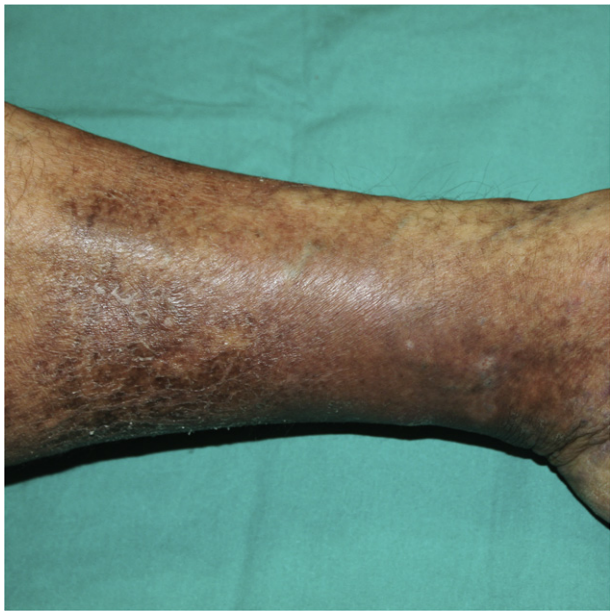

Fig. 7 Poikiloderma of Civatte, telangiectasia, atrophy, and macular hypopigmented and hyperpigmented areas.

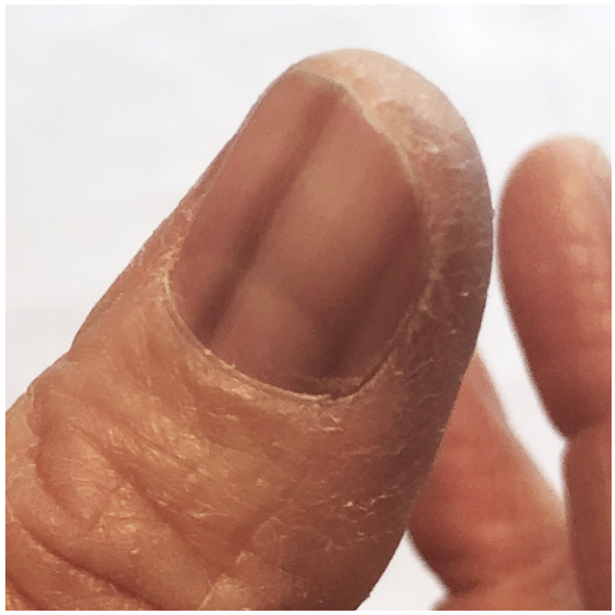

Fig. 8 Stasis dermatitis, brown hyperpigmentation on the leg.

hypertension is the main cause of skin changes in chronic venous disease. Reflux induced by incompetent valves, venous outflow obstruction, or failure of the lower extremity muscle pump are main causes of venous hypertension.[125–128] In one study, it was shown that leukocytes accumulate in the leg under high venous pressure conditions. Inflammatory changes as a result of leukocyte aggregation cause skin changes.[129] Extravascular accumulation of fibrin caused by chronic venous insufficiency probably induces tissue fibrosis and blocks the diffusion of oxygen to the upper epidermis and produces skin changes.[130] Matrix metalloproteinases produced by inflammatory cells, such as macrophages, can lead to breakdown of the extracellular matrix, impair healing, and skin changes.[128]

Clinical features

Stasis dermatitis typically presents with erythematous, scaling, and eczematous patches or plaques of the lower legs, classically involving the medial malleolus (Figure 8). In the chronic phase of stasis dermatitis lichenification, brown hyperpigmentation and scaling are seen in the medial malleolus. Hyperpigmentation occurs as a result of hemosiderin deposition, the breakdown product of hemoglobin from extravasated red blood cells known as hemosiderosis.[128–131] The histopathologic findings in SD are nonspecific. Histopathologic findings in the epidermis include hyperkeratosis, parakeratosis, spongiosis, and acanthosis. The findings in the dermis include extravasated erythrocytes, hemosiderin-laden macrophages, perivascular lymphocytic infiltration, dermal fibrosis, and proliferation of dilated small blood vessels. Stasis dermatitis may be misdiagnosed as cellulitis in the differential diagnosis. Contact dermatitis and PPD are also included in the differential diagnosis.[128]

Treatment

The main purpose is treating the venous hypertension. In most cases, nonpharmacologic measures such as leg elevation and compression bandaging are recommended. Topical steroids, pentoxifylline, flavonoids, and oxyrutein are used in pharmacologic treatment. Surgery can be performed in severe cases.[132]

Addison disease

Background

Addison disease is a rare endocrine disorder, with several oral and systemic manifestations. Hyperpigmentation is associated with the disease, oral pigmentation is seen as the first sign and develops earlier than skin pigmentation. It is described by Thomas Addison (1793-1860).[134] Hyperpigmentation is generally more prominent on the oral mucosa, areolas, anogenital area, scars, pressure points (such as the elbows and knees), and sun-exposed skin (such as the face, neck, and the dorsum of the hand).[133,134]

Etiopathogenesis

The clinical manifestations and signs of adrenal insufficiency depend on the rate and extent of loss of adrenal function, whether mineralocorticoid production is preserved, and the degree of stress. The onset of adrenal insufficiency is often very gradual, and it may go undetected until an illness or other stress precipitates adrenal crisis. Causes of primary adrenal

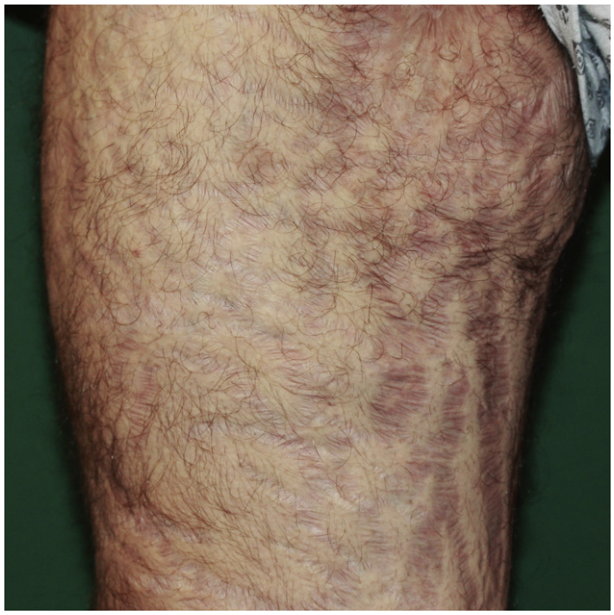

Fig. 9 Cushing syndrome with multiple striae on the leg.

insufficiency include **autoimmune adrenalitis, infectious diseases and agents** such as tuberculosis, fungal infections, cytomegalovirus, *Mycobacterium avium*, *Mycobacterium intracellulare*, syphilis, and African trypanosomiasis, malignancies, hemorrhages, and drugs.[135]

Hyperpigmentation of the skin and mucous membranes is caused by the stimulant effect of excess adrenocorticotropic hormone (ACTH) on the melanocytes to produce melanin. The hyperpigmentation is caused by high levels of circulating ACTH that bind to the melanocortin 1 receptor on the surface of dermal melanocytes. Other MSHs produced by the pituitary and other tissues include α-MSH (contained within the ACTH molecule), β-MSH, and γ-MSH.

Diagnosis

The diagnosis of adrenocortical insufficiency rests on the assessment of the functional capacity of the adrenal cortex to synthesize cortisol. This is accomplished primarily by use of the rapid ACTH stimulation test. Physical findings include hyperpigmentation of the skin and mucous membranes, decreased pubic and axillary hair in women, vitiligo, dehydration, and hypotension. Oral mucous membrane hyperpigmentation is pathognomonic for the disease.[136,137] Hyperpigmentation is most often prominent on the sun-exposed areas of the skin, extensor surfaces, knuckles, elbows, knees, and scars formed after the onset of disease. Palmar creases, nail beds, mucous membranes of the oral cavity (especially the dentogingival margins and buccal areas), and the vaginal and perianal mucosa may be similarly affected.[138] Other skin findings include vitiligo, which most often is seen in association with hyperpigmentation in idiopathic autoimmune Addison disease. It is due to the autoimmune destruction of melanocytes.

Treatment

The goals of pharmacotherapy are to reduce morbidity and to prevent complications. Hydrocortisone which has both glucocorticoid and mineralocorticoid properties, is the drug of choice for steroid replacement in acute adrenal crisis and for daily maintenance. Dehydration and mineral imbalance should also be avoided.

Cushing syndrome

Cushing syndrome occurs as a result of the inappropriate exposure of glucocorticoids to tissues for an extended period. It is described by Harvey Williams Cushing (1869-1939).[139] It can be from increased endogenous production also. In this syndrome, hyperpigmentation is frequently seen on the dorsal surface of the hands and feet, old scars, the face, the genitals, and the periumbilical area.[140]

Epidemiology

The exact incidence and prevalence of Cushing syndrome are not known. The prevalence of the syndrome is highly variable across different ethnic and cultural groups.[141]

Pathogenesis and etiology

There are two main etiologies of Cushing syndrome: endogenous and exogenous hypercortisolism. The most common cause of Cushing syndrome is exogenous hypercortisolism. Endogenous Cushing syndrome results from excessive production of cortisol by adrenal glands.[142] The excess of cortisol results in an increased rate of gluconeogenesis, glycogenolysis, and increases insulin resistance. The prolonged catabolism of proteins causes purplish striae of the torso.[143]

Clinical features

Dermatologic examination of the patient will show increased fat deposits in the upper half of the body causing buffalo hump, characteristic moon facies, acne, hirsutism, facial plethora, paper-thin skin, and wide vertical purplish abdominal striae. Buffalo hump is due to the fat redistribution. Fullness of the cheeks is known as moon facies. Multiple striae are seen especially on abdomen, flanks, arms, and thighs (Figure 9). Minor traumas can cause the formation of purpura with due to reduced connective tissue support. Ecchymoses may be present. Patients may have telangiectasias. Steroid acne, consisting of papular or pustular lesions over the face, chest, and back, may be present. These acneiform lesions are uniform in character.

Treatment

The 24-hour urinary cortisol estimation is the best diagnostic test for Cushing syndrome. Tapering off steroids slowly is the best therapy in iatrogenic Cushing syndrome. In case of Cushing disease, the best treatment is the surgical resection of pituitary adenoma.[144]

Brown-colored nipple during pregnancy

A lot of physiologic changes can be seen during pregnancy. Although some of them are very common, such as hyperpigmentation, others are more rarely associated like nail changes. Hyperpigmentation is very common during pregnancy, occurring in up to 90% of women.[145] Hyperpigmentation may be noted with darkening of areas that are already normally pigmented, with the nipple being most prominent (Figure 10). The pathogenesis is unclear, but the pigmentation is attributed to an increase in the MSH, estrogen, and progesterone serum levels.[146] The majority of changes spontaneously regress after delivery.[147]

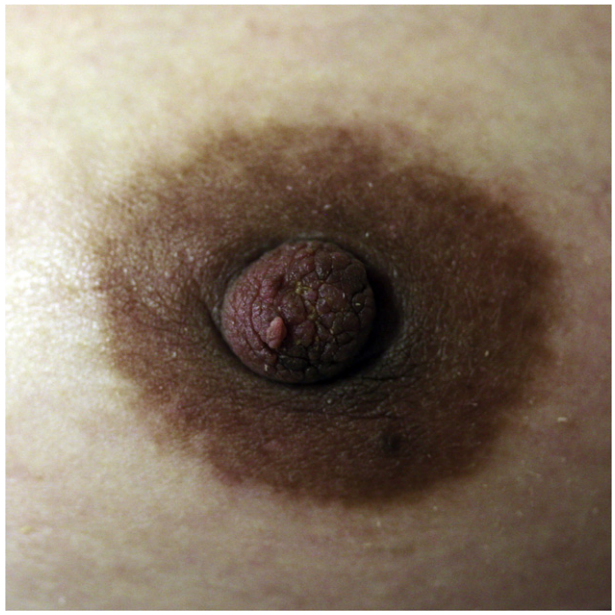

Fig. 10 Hyperpigmentation on the nipple during pregnancy.

Brown discoloration of nail plate

Etiology

Inspection of the nail for brown coloration can reveal a variety of conditions such as onychomycosis and incontinentia pigmenti. Brown discoloration of the nail may be caused by pigments of melanocytic or nonmelanocytic origin.

Nail pigmentations of nonmelanocytic origin are termed as nail dyschromia or hyperchromia. Brown dyschromia of the nail occurs due to exogenous pigmentations, nail infections, and subungual hematoma. Exogenous causes of nail dyschromia include topical medications such as silver nitrate and ethacridine lactate, cosmetics, and tobacco. Fungal and bacterial infections may lead to nail dyschromia. Infections with *Trichophyton rubrum* or with dematiaceous pathogens such as *Scytalidium dimidiatum* are responsible for brown to black nail hyperchromia. Diagnosis of onychomycosis should be based on mycologic tests, not on sole clinical inspection.[148,149] Dermatoscopy provides valuable information to differentiate subungual hematoma from other causes of nail pigmentation. Presence of a homogenous color, peripheral fading and globular pattern are typical dermatoscopic features of this frequent condition.[150,151]

Clinical features

Melanonychia, also known as longitudinal melanonychia or melanonychia striata, presents with brown or black longitudinal bands of pigmentation (Figure 11). The condition may be due to melanocytic activation or melanocytic hyperplasia. Hyperplasia of the melanocytes is mostly caused by lentigo or nevi. Subungal melanoma, a rare subtype of melanoma in white people, should always be kept in mind in the differential diagnosis. Pigmentations of unknown cause or unexplained hematomas warrant a biopsy to exclude melanoma. Hutchinson sign defined as pigmentation of the cuticle and proximal nail fold may be seen in some of the melanoma patients, especially in advanced stages. The poor prognosis of subungal melanoma is mostly attributed to delayed diagnosis. Longitudinal melanonychia by melanocytic activation is characterized

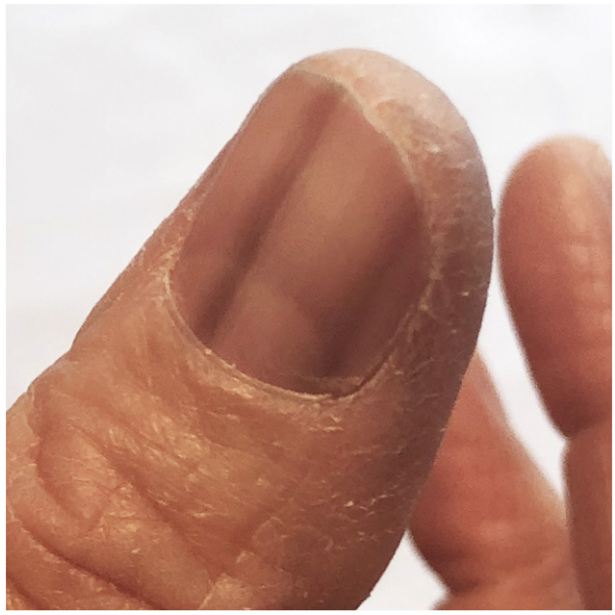

Fig. 11 Melanonychia striata, brown-black longitudinal bands of pigmentation.

by normal number of melanocytes and accounts for 73% of single longitudinal melanonychia in adults. Physiologic causes such as racial predisposition or pregnancy, chronic trauma, and underlying dermatologic or systemic diseases are related to melanocytic activation. Inflammatory diseases such as psoriasis and nail lichen planus, along with nail tumors such as Bowen disease and onychopapilloma are the most common dermatologic conditions associated with melanonychia. Among systemic diseases endocrinopathies such as hyperthyroidism, Cushing syndrome and Addison disease may lead to nail dyschromia.[148,149] Transverse orange-brown discoloration of the fingernails and toes is a relatively new nail change reported in Kawasaki disease.[153] Local trauma due to tight shoes or nail biting can also be responsible for melanonychia. Symmetrical pigmentation of lateral and external sides of the fourth and fifth toenail is typical involvement sites of frictional melanonychia which occurs due to overriding toes or ill-fitting shoes. Iatrogenic causes of melanocytic activation include drugs, x-ray exposure, phototherapy, and electron beam therapy.[154] Brown discoloration of the nails may also occur as a side effect of various drugs, such as hydroxyurea, methotrexate, fluconazole, zidovudine, cyclophosphamide, etc.[150,152,155,156] Laugier-Hunziker syndrome, an acquired mucocutaneous pigmentary disorder without systemic involvement, starts in adulthood. Along with hyperpigmented macules involving lips and oral cavity, Laugier-Hunziker syndrome may lead to one or several longitudinal melanonychias on fingers. Peutz-Jeghers syndrome share similar clinical features with Laugier-Hunziker syndrome, however the onset of mucosal pigmentations is during childhood period and the disease is autosomal dominantly inherited. The importance of Peutz-Jeghers syndrome is the association of the syndrome with intestinal polyposis and intestinal malignancies. Perioral involvement is a diagnostic clue for Peutz-Jeghers syndrome.[152]

Cutaneous T-cell lymphoma, especially in advanced stages, may be associated with nail alterations. Recognition of nail abnormalities is important as they may predict disease recurrences. Yellow-brown discoloration, crumbling, onycholysis, and onychomadesis are the most commonly reported clinical manifestations.[157] Cutaneous Langerhans cell histiocytosis is a rare clonal disease of dendritic Langerhans cells. Nail involvement in form of onycholysis and subungal hyperkeratosis has been reported and is associated with poor prognosis.[158]

Acrokeratosis paraneoplastica, also known as Bazex syndrome, is characterized by psoriasiform eruptions of acral body parts along with nail changes. Recognition of this rare syndrome is important as it is associated with squamous cell carcinomas of upper airways and gastrointestinal system. Nail involvement is typified by yellowish-brown discoloration, subungal hyperkeratosis, onycholysis, ridging and onychomadesis.[159,160]

Incontinentia pigmenti is a hereditary, systemic disease typically manifesting itself with cutaneous lesions along Blaschko lines. Nail alterations such as dystrophy, pitting, onychogryphosis, yellow discoloration, subungual tumors, and periungual keratotic tumors have been reported.[161] Inflammatory linear verrucous epidermal nevus may lead to nail dystrophy when lesions extend from the extensor surface of the limb onto the nail.[162]

Treatment

Approach to a brown discoloration of the nail consists of through history taking, clinical examination, and dermatoscopic examination. History reveals whether the pigment is congenital or acquired and its duration along with clues to diagnosis such as physical activities, recent trauma, and the culprit drugs. Clinically, all 20 nails, periungual region, and oral and genital mucosae should be inspected. Mucosal pigmentations are features of Peutz-Jeghers syndrome and Laugier-Hunziker syndrome. Size and color homogeneity of the lesion should be noted. Nail dermatoscopy helps in differential diagnosis of brown discoloration of the nail is best performed using an ultrasound gel. Gray-pigmented bands mostly point to conditions without hyperplasia of the melanocytes; brown-pigmented bands occur due to melanocytic hyperplasia. Brown bands with irregular spacing and disruption of parallelism is alarming for melanoma. Lastly, free edge of the nail should be evaluated with dermatoscopy to define the origin of nail pigmentation. Pigment located in upper and lower portion of the nail is produced in proximal and distal nail matrix, respectively. Biopsy should be obtained from lesions showing irregular pattern on dermatoscopy. Clinically, sudden appearance of a pigmentation or sudden changes in preexisting pigmentations, isolated pigmented band occurring at fourth to sixth decade of life, acquired pigmentations of the thumb, index finger, or large toe, presence of nail destruction accompanying pigmentation and presence of Hutchinson sign should be considered for biopsy. Histopathology is gold standard in these cases with suspicion of malignancy.[163]

Conclusions

Brown diseases are mostly acquired conditions with unclear etiologies. Often the differential diagnoses of brown diseases are important, as they may be a clue to underlying systemic conditions. Some brown diseases, such as PPDs, PIH, and poikiloderma of Civatte may require treatment for the unacceptable cosmetic appearance.

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