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Hair, nail, and pigment changes in major systemic disease

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Abstract In this article, the nail, hair, and pigment changes caused by systemic diseases will be reviewed. Among the subjects discussed are abnormalities of shape, attachments, surface, and color of the nails; hair alterations such as telogen and anagen effluvium, scarring alopecia, hypertrichosis, and hirsutism; and pigment changes due to connective tissue disorders, sarcoidosis, and metabolic and endocrinologic diseases, among others.

Introduction

Nail and hair are adnexal structures of the skin, and the careful examination of these elements can provide important clues to systemic diseases. More often, these clues are nonspecific pattern reactions, although occasionally, they can be more helpful in suspecting a specific diagnosis. When facing an abnormality of the nail or hair, it is important to examine the rest of the skin, obtain a detailed history of prior events, and question about associated systemic symptoms.

Nail alterations in systemic disease

The nail is an apparatus that provides a strong keratinous plate over the dorsal surface of each digit. Its components are nail plate, nail bed, nail matrix, and nail folds. The nail apparatus is biochemically and kinetically active throughout life, different from the hair follicle, which undergoes periods of quiescence.

The nail plate is generated by the nail matrix localized at the proximal region of the nail bed. As the nail grows, the distal part of the matrix contributes to the formation of the deeper layers of the plate. As consequence, a disruption of the distal nail matrix may produce problems in the deeper layers (ridging or splitting); and if the disturbance occurs in the proximal nail matrix, the problem will be more superficial (pitting). A transient problem tends to form transverse lines across the nail plate[1]; and when these changes are seen on the nail plate, it is possible to determine approximately when the systemic condition occurred, knowing that the fingernail grows about 0.1 to 0.15 mm/d and toenails at one third of this rate.[2]

Abnormalities of shape

Clubbing

Clubbing is defined as an increased transverse and longitudinal nail curvature, hypertrophy of the soft tissue components of the digital pulp, and hyperplasia of the fibrovascular tissue at the base of the nail.[2] Some of these changes also involve the terminal digital phalanges, giving the distal digit a bulbous appearance. The most used approaches for identifying clubbing on physical examination are visual inspection and palpation of the cuticle for

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increased sponginess, although authors have described more accurate methods to confirm the presence of this alteration. Lovibond defined the *profile's sign* of the thumb, or the *Lovibond angle* as it came to be known, as the angle formed by the nail as it exits the proximal fold. The normal angulation would be of less then 180°; and in clubbing, this angle is greater than 180°. Other methods of detecting the presence of clubbing have been described, such as the "Schamroth sign," the modified profile sign, the hyponychial angle, and the distal phalangeal to interphalangeal depth ratio.[3] The published criteria for the diagnosis of clubbing were reviewed; and it was recommended that, in cases of diagnostic uncertainty, the profile angle and the distal phalangeal to interphalangeal depth ratio may be used to better characterize the presence of clubbing.[4]

Multiple hypotheses of the pathophysiology of clubbing have been proposed over the years. The most promising hypothesis is based on emerging evidence of the physiology of platelet production, which showed that megakaryocytes are normally fragmented into platelets in the lungs. When there is a process that disrupts the normal pulmonary circulation, the megakaryocytes are allowed to enter the systemic circulation. Because of their large size, they become impacted in the fingertip circulation and then are activated to release cytokines and chemokines that initiate the mechanism that will end with clubbing formation.[3]

Clubbing can be familial, idiopathic, or acquired. It may appear as an isolated finding or may occur as part of the syndrome of hypertrophic osteoarthropathy. Hypertrophic osteoarthropathy is characterized by periostosis of long bones, joint pain, and clubbing; it may be primary, also known as *pachydermoperiostosis*, or secondary to a variety of disease processes.

The acquired or secondary forms of clubbing or hypertrophic osteoarthropathy can be unilateral or bilateral. Unilateral clubbing has been associated with neurologic and vascular diseases such as hemiplegia, dialysis fistulas, Takayasu arteritis, and others. The most known association between bilateral clubbing and systemic diseases is with pulmonary neoplasms; but it can also occur in other conditions involving the cardiac, gastrointestinal, and endocrine systems and in infectious, other neoplastic, psychiatric, and multisystem diseases as well.[3]

Once the diagnosis of clubbing is established, a complete history and physical examination will allow the clinician most of the time to narrow the differential diagnosis. An algorithm for evaluation of clubbing was recently proposed,[3] and the finding of clubbing without obvious associated disease should prompt a search for bronchogenic carcinoma or another occult disease.[1]

Koilonychia

Koilonychia is represented as a transverse and longitudinal concavity of the nail, resulting in a "spoon-shaped" nail. The pathophysiology of this peculiar shape is not understood. Historically, this condition is linked with iron deficiency, although this association has been questioned in many studies. Indeed, koilonychia has even been reported in hemochromatosis. Some authors sustain that a dietary deficiency of proteins, notably sulfur-containing amino acids, is the likely cause of nutritional koilonychia and also some conditions such as hyperthyroidism, in which the increased metabolic rate promotes the gradual exhaustion of structural amino acids.[5]

Koilonychia has been reported as being idiopathic, familial, or acquired. The acquired form of koilonychia comprises a large group of conditions that can cause this alteration. As discussed above, the classic association of koilonychia occurs with anemia due to iron deficiency; but this abnormality can occur in various other systemic conditions.[2]

Pincer nail

Pincer nail is a dystrophy characterized by transverse overcurvature that increases along the longitudinal axis of the nail plate and reaches its greatest proportion at the distal part. Pincer nail can be hereditary or acquired. Acquired pincer nail may be due to numerous dermatoses (the most common is psoriasis), tumors, or continuing trauma of the nail apparatus. There have also been reports of association of pincer nail deformity with β-blocker use, arteriovenous fistula placement in the forearm,[6] metastasizing adenocarcinoma of the sigmoid colon, systemic lupus erythematosus,[7] and after Kawasaki disease.[8]

Macronychia and micronychia

Macronychia and micronychia are conditions where a nail is considered too large or too small in comparison with other nails or nearby digits. The nail disorder is usually associated with an abnormal digit. These conditions are often seen in endocrine disorders such as acromegaly, a disease in which either macronychia or micronychia can occur. In case of micronychia, it is unclear whether it is true micronychia or simply the illusion of smaller nails due to growth and hypertrophy of the soft tissue of the fingers. In hyperparathyroidism, a pseudoracquet nail can be seen. These nails appear broader and shorter than normal because of acroosteolysis of the distal phalanxes due to calcium mobilization.[9]

Abnormalities of nail attachment

Onycholysis

Onycholysis is the separation of the nail plate from the nail bed, which can occur at any point of the nail and generally is accompanied by a discoloration of the affected area (Fig. 1).

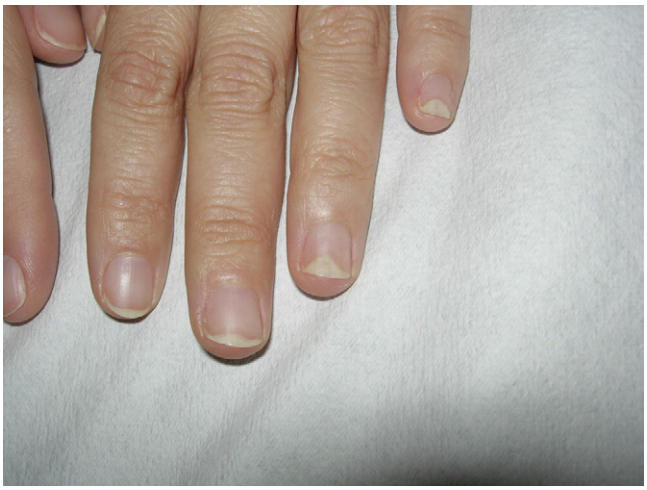

Fig. 1 Onycholysis.

Onycholysis is most commonly due to local factors such as fungal nail infections, tumors near or at the nail apparatus, or even secondary to trauma. Onycholysis in association with systemic conditions has been reported in thyroid diseases, most commonly hyperthyroidism (also known as *Plummer nail*) but also hypothyroidism, pellagra, porphyria, and syphilis. Another common cause of onycholysis is the use of systemic medications including chemotherapy.[2,9]

Pterygium

Pterygium of the nail describes the formation of a central fibrotic band that divides the proximal nail into 2 parts. The fibrotic band emerges more commonly from the proximal nail fold. There are a few reports of this abnormality associated with systemic diseases such as graft-vs-host disease and reactional leprosy.[10,11]

Pterygium inversum unguis is an uncommon nail abnormality in which the distal nail bed adheres to the ventral surface of the nail plate with obliteration of the distal nail grove. Most of the acquired pterygium inversum unguis cases have been described primarily in patients with connective tissue diseases, especially systemic sclerosis and lupus erythematosus. There have been very few reports of cases associated with leprosy and after stroke.[12]

Abnormalities of nail surface

Longitudinal grooves

Longitudinal striations are accentuated ridges in the nail surface that can occur normally in the elderly (Fig. 2). When the nail is also thin and lusterless, the condition is called *trachyonychia*. These alterations can occur in all nails, configuring a 20-nail dystrophy. In this situation, associated conditions, including alopecia areata, psoriasis, atopic dermatitis, and lichen planus, must be considered.[13] Trachyonychia also may be seen in patients with vitiligo,[14] and longitudinal nail ridge may accompany osteoarthritis of the hand.[15]

A nail longitudinal red streak is called *longitudinal erythronychia* and may have several causes. It has a corresponding band of thinned nail plate as part of the defect. Longitudinal erythronychia can be multiple or localized. Multiple lesions typically indicate an inflammatory disease such as lichen planus. When localized, they may be a single or bifid streak arising through a benign or malignant neoplasm (Bowen disease, basal cell carcinoma, or squamous cell carcinoma), scarring of the dermis or epidermis, or the first stage of an inflammatory process that may evolve into multiple longitudinal erythronychia.[16-18]

Transverse grooves

Two types of transverse changes can be seen: those that actually incorporate into the nail plate and those that are seen on the nail bed. The lesions in the nail plate do not change if pressure is applied, but the lesions of the nail bed do change. Endogenous or systemic conditions generally cause transverse changes that follow the shape and contour of the lunula. Exogenous conditions follow the shape and contour of the proximal nail fold.[2] Lesions in the nail bed produce changes predominantly in color and will be discussed later.

Grooves and pits are indication of injury to the nail matrix. Transverse linear depressions in the nail plate are called *Beau line* and may be caused by any disease severe enough to disrupt normal nail growth. They can also be caused by trauma or exposure to cold temperature in patients with Raynaud disease.[1]

Pitting

Pitting is the presence of small pinpoint depression in an otherwise normal nail plate. These pits are the result of an

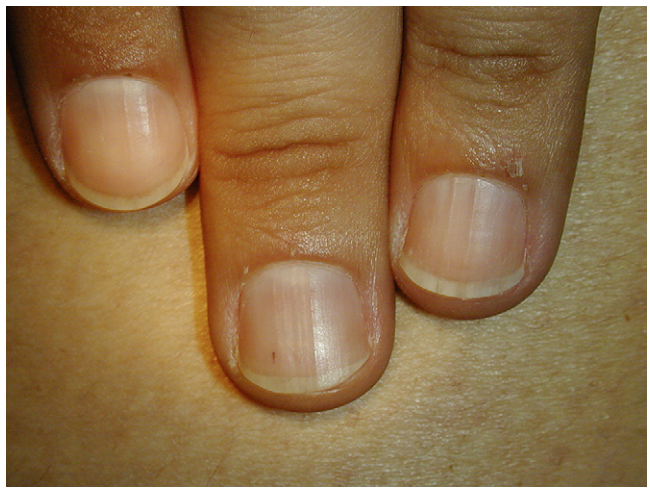

Fig. 2 Longitudinal grooves.

alteration of the proximal nail matrix, which generates the more superficial layer of the nail plate. Any alteration in this region can cause pits. More commonly associated with psoriasis, pits can occur associated with Reiter syndrome, sarcoidosis, alopecia areata, pemphigus vulgaris, rheumatoid arthritis, lichen planus, and syphilis and also may appear in healthy persons.[19]

Onychoschizia

Onychoschizia is characterized by transverse splitting into layers at or near the free edge of the nails, which can result in discoloration because of sequestration of debris between layers. It is seldom associated with systemic disorders, although it has been reported with human immunodeficiency virus infection and glucagonoma.[20,21]

Brittle nails

Brittle nail is a heterogeneous abnormality characterized by increased fragility of the nail plate. Clinical features of brittle nail syndrome are onychoschizia and onychorrhexis. This condition is more commonly due to exogenous factors such as frequent immersion in water, contact with chemical products, and trauma. Some systemic diseases may cause this alteration, especially metabolic and endocrine conditions such as hypopituitarism, hypothyroidism and hypoparathyroidism, acromegaly, diabetes mellitus, gout, osteoporosis, arginosuccinic aciduria, and malnutrition.[22]

Abnormalities in nail color

Leukonychia

Leukonychia is defined as opaque white coloring in the nail plate (Fig. 3). It can be seen in multiple patterns: punctata, striata, partialis, and totalis. The leukonychia punctata and striata are commonly seen as reactions to trauma, even minor ones (manicure, for example). Leukonychia caused by systemic conditions is most commonly partialis or totalis. Partial leukonychia has been reported with systemic diseases such as tuberculosis, nephritis, Hodgkin disease, metastatic carcinoma, or leprosy. Leukonychia totalis may be hereditary or related to systemic conditions such as ulcerative colitis, typhoid fever, cirrhosis, and leprosy.[2]

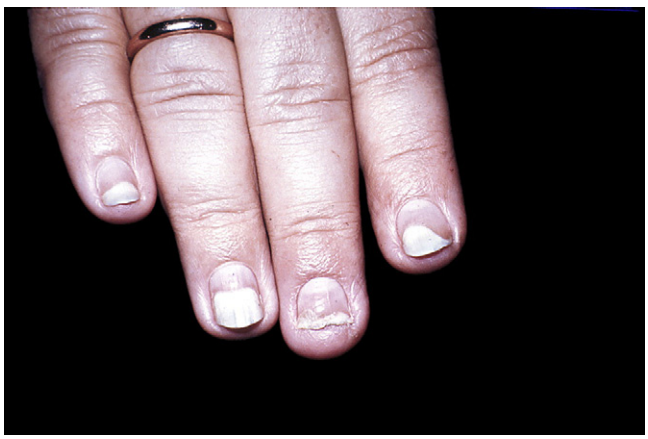

Fig. 3 Leukonychia.

Transverse leukonychia is also known as *Mees lines* and has been reported to be a sign of arsenic poisoning; but they are also reported to be present in other systemic conditions such as septicemia, dissecting aortic aneurysm, chronic renal failure, congestive heart failure, and Hodgkin disease and as a result of some medications, particularly chemotherapy.[2,19]

Melanonychia

When the nail shows a band of longitudinal black or brown pigmentation, it is called *melanonychia* (Fig. 4). Their presence can be a normal finding in the nails of dark-skinned persons, occurring in more than 77% of blacks older than 20 years.[19] These findings must always be differentiated from subungual melanoma, which sometimes is doable only with biopsy. Pigmentation of the nail has been reported to be in association with acanthosis nigricans, Addison disease, Peutz-Jeghers syndrome, and AIDS and secondary to medications.[2,19]

Muehrcke white bands

These bands are located in the nail bed parallel to the lunula, with a pink band between 2 white lines. They are commonly associated with hypoalbuminemia and tend to disappear after the correction with albumin infusion. Because the lesion is in the nail bed, it does not follow the growth of the nail and vanishes when pressure is applied to the nail plate. These nail bed changes have also been reported to occur after heart transplant and chemotherapy.[2,19,23]

Half-and-half and Terry nail

In half-and-half nails or Lindsay nails, the proximal portion of the nail bed is white and the distal portion (20%-60%) is pink or reddish brown, with a sharply demarcated contrast between the 2 zones. It is seen more commonly in patients with chronic renal failure and has been described in one third of patients with azotemia, with no correlation with uremia's severity.[24] The proximal nail fold appears white because of edema of the nail bed and capillary network. This abnormality is also described in patients with Kawasaki disease, liver cirrhosis, and zinc deficiency. More recently, 4 cases of half-and-half nails associated with Crohn disease were described.[25]

Terry nail is similar but is characterized by a white discoloration of the proximal part of the nail bed, leaving an exaggerated pink-brown discoloration of the 1- to 2-mm free

Fig. 4 Melanonychia.

edge of the nail. Terry nail has been reported in patients with liver cirrhosis, chronic congestive heart failure, or adult-onset diabetes mellitus.[26]

Yellow nail syndrome

The yellow nail syndrome is rare and characterized by a triad of slow-growing dystrophic yellow nail, lymphedema, and pleural effusions, often associated with pericardial effusion, rhinosinusitis, and bronchiectasis. The etiology of this syndrome is obscure, although its pathogenesis seems to involve impaired lymphatic drainage.[27] Other researches suspect that yellow nail syndrome may be related to protein leakage from increased microvascular permeability, which would account for its common association with hypoalbuminemia.[28]

Hard, thick, and curved nails diffusely pale yellow to dark yellow-green in color are the clinical features in this syndrome. The nail plate becomes opaque, and the lunula is not seen. Most patients complain that their nails do not grow. There is loss of the cuticle and an increased prevalence of paronychia. Yellow nail changes often precede the pulmonary abnormalities and have been reported as a paraneoplastic process in various types of carcinoma.[2]

Red lunula

Erythema of part or all of the lunula may affect all digits, but most prominently the thumb. Red lunula has been described in patients with cardiovascular, endocrine, gastrointestinal, hematologic, hepatic, infectious, neoplastic, neurologic, pulmonary, renal, and rheumatologic disorders and thus are a nonspecific alteration.[29]

Hair alterations in systemic diseases

Hair has no vital function in humans, yet its important psychologic functions are recognizable in most people. In contrast to what was described above for the nail units, the hair follicles show intermittent activity. Each hair has a period of growth followed by a period of retention in the follicle without growing and is eventually shed and replaced for another growing hair. The knowledge of this repetitive sequence of growth and rest, known as the *hair cycle*, is important in understanding hair abnormalities, especially those related to systemic diseases. The count of the hair shedding daily is necessary to establish a shedding or thinning pattern.

The period of hair growth is the anagen phase, and the duration of this phase is responsible for the final length of hair. Under normal circumstances, 80% to 90% of hair follicles on the human scalp are in anagen at any one time. At the end of anagen, the follicle enters an involutionary, very short phase known as *catagen*, with only 1% of the scalp follicles in this phase. The period between the completion of follicular regression and the beginning of the next anagen phase is termed *telogen*. Approximately 10% of the scalp follicles are in this phase, which lasts an average of 100 days.

Hair loss may be idiopathic, associated with aging, related to a genetic predisposition, caused by drugs, or associated with metabolic and hormonal abnormalities. The patients must be submitted to a meticulous clinical examination and review of the personal and family histories, diet and medication, and hair care habits. Laboratory tests can be performed to look for chronic diseases such as diabetes, renal or hepatic pathology, diminished albumin, or iron storage.

Telogen effluvium

In humans, synchronous hair growth disappears in very early ages; and each hair follicle cycle is independent of the other follicles. As a consequence, humans tend to lose a few hairs each day; and a fairly uniform density of hair is maintained at all times. Hair density on the scalp varies from person to person, with most people having about 100,000 hairs. Extrapolation of the trichogram data with the percentage of telogen hairs and knowing that this phase lasts about 3 months have led to the assertion that people must shed about 144 hairs per day.[30]

When an abnormally large number of hairs enter the telogen phase simultaneously, it causes a hair loss termed *telogen effluvium*, which is by far the most common form of hair loss seen in systemic disease.[31] Because of the duration of the telogen phase, when there is a definable precipitating event, hair loss begins approximately 3 months later. This is the classic description for telogen effluvium, or acute telogen effluvium; but 5 other mechanisms were described for increased club hair shedding,[32] 2 of which are more relevant to telogen effluvium related to systemic conditions: immediate anagen release and delayed anagen release.

Telogen effluvium is caused by any disruption of the hair cycle that results in increased or synchronized telogen

shedding. A trigger for this perturbation can often be found in the history, especially in cases of acute telogen effluvium.[32] The most common trigger factors are febrile illness, major surgery or hemorrhage, starvation, and emotional stress, although this last one is controversial. In about 33% of cases of acute telogen effluvium, no trigger can be identified. The mechanism of the acute form of telogen effluvium is immediate anagen release.[30]

This mechanism is also responsible for the telogen effluvium due to medications, which occurs more commonly with the use of retinoids, anticonvulsants, antithyroid medications, anticoagulants, and β-adrenergic blocking agents.[31]

The second mechanism described for the telogen effluvium is delayed anagen release, which typically occurs in women who are 2 to 5 months postpartum. In this case, the telogen effluvium is due to the prolongation of anagen phase that occurs during pregnancy; and it is considered a physiologic process.[31,32]

A short-lived insult usually produces a sudden onset of diffuse shedding. If the insult is prolonged or repeated, shedding can develop insidiously. *Chronic diffuse telogen hair loss* refers to telogen hair shedding persisting longer than 6 months. Accepted causes of chronic diffuse telogen hair loss are thyroid disorders, profound iron deficiency anemia, acrodermatitis enteropathica, and malnutrition. Hyperthyroidism and hypothyroidism cause a diffuse telogen hair loss in approximately 50% and 33% of patients, respectively. The mechanism of telogen hair shedding in thyroid disorders still remains unclear.[30]

Anagen effluvium

Anagen effluvium occurs when metabolic and mitotic activity of the follicular epithelium is rapidly suppressed. The hair shaft markedly thins and tapers to a point, like the tip of a sharpened pencil, while the follicles are still in the anagen phase of the hair cycle. Dramatic hair loss occurs shortly after the metabolic insult, within days or weeks of precipitating factors.[31,33] Systemic chemotherapeutic agents such as colchicine, high doses of radiation therapy, and toxic substances such as thallium, although acting in different ways, all cause an anagen arrest.[31,33] Certain inflammatory diseases are also capable of diminishing the metabolic activity of hair follicles, resulting in anagen effluvium.[31,33] One example is alopecia areata (Fig. 5), an autoimmune T-cell–mediated disease targeted against hair follicle antigens, whose exact mechanism remains a mystery.[34] Many systemic diseases characterized by peribulbar inflammation, such as systemic lupus erythematosus, syphilis secondary, and others, can result in anagen arrest.[31] In the course of anagen arrest, a hair pull will extract numerous dystrophic shafts with pencil-point hairs often losing pigmentation in the process. When the pathologic process or treatment is stopped, the hair growth should resume. If the stem cells of the follicle are injured, the follicle may disappear.

Scarring alopecia

Several systemic diseases cause scarring alopecia by destruction of hair follicles with the obliteration of follicular orifices and its replacement by fibrous tissue. It occurs in the lesions of discoid lupus erythematosus, resulting in permanent hair loss.[31] Scarring alopecia has also been reported in dermatomyositis. In systemic diseases with blood supply alteration, direct compression, or release of injurious cytokines, follicles are permanently destroyed. These processes may occur in the granulomatous infiltrate of sarcoidosis, primary systemic amyloidosis, and scleroderma.[31] Certain infections such as cutaneous tuberculosis, Hansen disease, tertiary syphilis, and leishmaniasis can also cause scarring alopecia.

Scalp metastasis of internal cancer can cause neoplastic alopecia, with a still unclear exact pathogenesis. It may be a result of physical compression from the tumor, reactive fibrosis, chemical mediators released by the tumor, reactive inflammation, or a combination of these factors.

Scarring alopecia is found in chronic graft-vs-host disease[35] and mycosis fungoides, where there are 2 types: the first is alopecia mucinosa; and the second, follicular mycosis fungoides.[31,33]

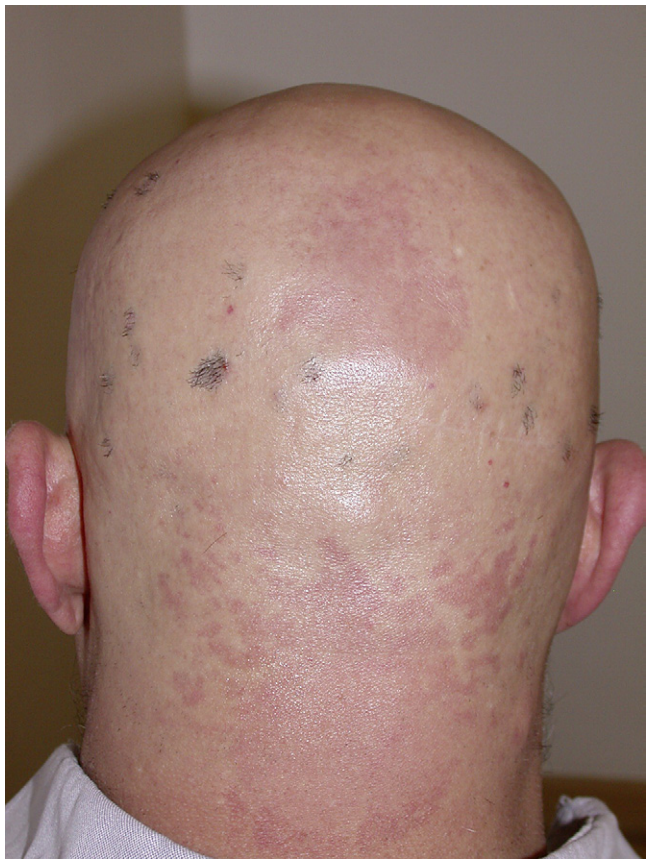

Fig. 5 Alopecia areata.

Hypertrichosis

Hypertrichosis is defined as an excessive growth of non–androgen-dependent hair. It may be localized or generalized, congenital, or acquired. It has been reported in association with multiple dermatologic syndromes, mostly congenital, and also with multiple sclerosis, schizophrenia, lipoatrophic diabetes, starvation, and anorexia nervosa. Hypertrichosis has been associated with many medications, but the most common are minoxidil and cyclosporine.[36]

Acquired growth of lanugo hair appears to be an important cancer marker. The hair is soft, silky, long, and unpigmented and covers the face, neck, trunk, and limbs.[31,37] Hypertrichosis is often found in sun-exposed areas of patients with porphyria.[31,38]

Hirsutism

Hirsutism is the presence, in women, of terminal and vellus hairs in a male pattern, related to growth of androgen level or to increase of end-organ response to androgens (Fig. 6). This condition may be idiopathic, reflect a familial trait, become prominent with aging, or be associated with adrenal or ovarian disease. Polycystic ovarian syndrome is the most common ovarian cause, whereas congenital adrenal hyperplasia is the most common adrenal cause.[39,40]

Pigment changes due to systemic diseases

Normal skin color is dependent on vascularization, carotenoids, and especially on melanin pigment. Pigmentation provides cosmetic coloration to the skin and protection from ultraviolet rays. The melanin pigment is synthesized and deposited within a melanosome—organelles that are transferred to keratinocytes—and recent knowledge in molecular biology helps us to know about the regulation of pigmentation of the skin by the environment. When under the stimulus of hormones such as melanocyte-stimulating hormone and adrenocorticotrophic hormone or when irritated, the production of melanosomes increases, converting tyrosine to melanin. More than 120 pigment genes have already been identified that affect visible color of the skin, hair, and eyes.[41,42] About 50% of them were cloned and had their functional level characterized, and most of them provide a model for understanding the mechanisms of human disease.[41,42]

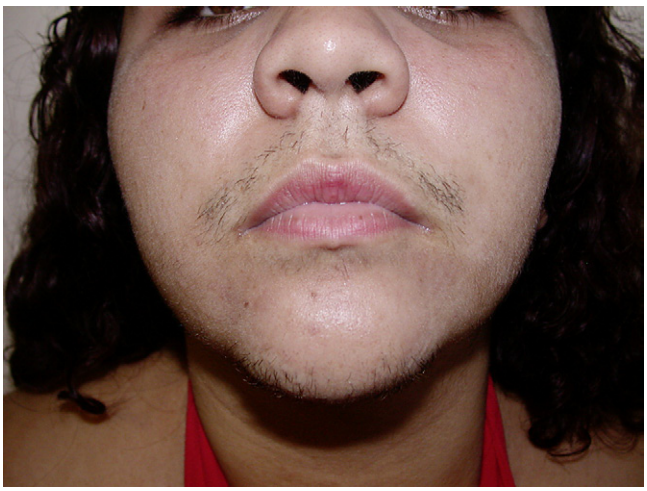

Fig. 6 Hirsutism.

The cutaneous pigmentary system is an important stress response element of the skin and protects the entire organism against noxious stimuli. The functional regulation of follicular and epidermal pigmentary unit by the melanocortin system can be found at the local and systemic levels.[43,44]

The cause of hyperpigmentation is the activity and presence of melanocytes. Diffuse hyperpigmentation may be induced by medications or systemic diseases such as hemochromatosis, hyperthyroidism, collagenosis, and Addison disease. In these cases, the pigmentation may disappear by discontinuing offending medications or after specific treatment.[45]

Hyperpigmentation in advanced age is accompanied by atrophy of the epidermis and of the appendices as well as degeneration within the corium, which cause asteatosis, purpura, and elastosis.[46]

Connective tissue disorders

Scleroderma, the abnormality in pigmentation, is reported in many publications. The diffuse hyperpigmentation shows an extensive pigment incontinent in the upper dermis. There is an increase of pigmentation in the sun-exposed areas such as dorsum of the hand and forearm.[47] In the other areas, there is pigment loss with only perifollicular pigment remaining, resembling repigmenting vitiligo.[48]

Lupus erythematosus is a spectral disease that varies from an acute fulminant disease with a few months' duration to a chronic smoldering process lasting more than 30 years. The skin may be the sole organ involved in a patient's lifetime, or skin may precede involvement of other systems by varied intervals. Skin discoid lesions evolve with partial or complete loss of pigmentation, hyperpigmentation, or both, frequently accompanying the development of atrophy. In systemic lupus erythematosus, there may be weight loss, weakness, pigmentation of skin, and altered liver tests.[48,49]

In dermatomyositis, pigmentary changes are secondary to chronic skin involvement, especially in certain parts of the body, such as the *V* area of anterior neck and upper chest, back, and buttocks, where the appearance of poikiloderma is indistinguishable from other causes of this multicomponent skin change.[50]

Sarcoidosis

One of the less common specific presentations of sarcoidosis that has been reported is hypopigmented lesions. It may develop over papules and nodules, or it may exist as patches that feel normal or slightly indurate.[51]

Metabolic and endocrinologic diseases

Systemic symptoms may indicate the presence of hyperthyroidism that causes a diffuse hyperpigmentation, especially in patients with darker complexions.[47] The most characteristic clinical signal of hypothyroidism is generalized myxedema resulting from of deposition of dermal acid mucopolysaccharides. Vitiligo has been associated with autoimmune thyroid disease, such as hyperthyroidism or hypothyroidism, or with Addison disease and others.[52]

Addison disease exhibits a diffuse hyperpigmentation with a "muddy" appearance, especially in sun-exposed areas, perineum, axillae, areolae, palms, and soles. There may be hyperpigmentation and vitiligo developing together in some patients. It is an adulthood disease; and it is accompanied by blood pressure instability, fatigue, anorexia, and depression. There is a relationship with elevated adrenocorticotrophic hormone and melanocyte-stimulating hormone levels.[47]

Hemochromatosis shows a diffuse slate gray or bronze hyperpigmentation in adults. It is not hormone related, there is no relationship with sun-exposed areas, and it is associated with multiorgan dysfunction caused by iron deposition.[47]

Acanthosis nigricans, is usually related to insulin resistance or obesity.[53] Hyperpigmentation has been reported rarely, whereas glucose intolerance is common in these patients.[47] Carotenemia is reported in more than half of diabetic patients and yellow skin in 10% of this population. Although carotene blood level is normal, it may have disproportionate accumulation in the skin or the skin color may not be caused by carotene but by dermal collagen glycosylation with yellow end-stage glycosylation products.[54]

In some presentations of diffuse cutaneous mucinoses, such as scleromyxedema and reticular erythematous mucinosis, the affected areas may exhibit erythema and brownish discoloration.[55]

Hyperpigmentation is one of the most evident features of porphyria cutanea tarda, and it is also common in patients with chronic renal failure who are anti–hepatitis C virus positive.[56,57] Chronic renal failure contributes to anemia, with resulting universal pallor of the skin. The deposition of carotinoids and urochromes leads to a yellow shading of the integument.[58] The mechanism of hepatitis C–inducing porphyria cutanea tarda is unknown, but there are 4 propositions: (1) decreased intracellular glutathione concentration, (2) decreased uroporphyrinogen decarboxylase activity, (3) elevated hepatocellular iron, and (4) production of an uroporphyrinogen decarboxylase inhibitor.[57]

Alkaptonuria is a rare metabolic disorder caused by homogentisic acid oxidase deficiency resulting in accumulation of homogentisic acid in collagenous structures. Bluish-black discoloration of connective tissues; arthropathy of large joints; cardiovascular abnormalities; and renal, urethral, and prostate calculi are the observed symptoms.[58]

The texture of the skin in hypopituitarism is smooth and coarse, with dryness and scaling; and the patients have a youthful appearance. The skin is pale and exhibits a decreased capacity to tan. In hyperpituitarism, excessive secretion of growth hormone produces gigantism. The skin is thickened because of an increase in the dermal collagen. Hyperpigmentation occurs in 40% of patients with acromegaly.[38]

Chronic active hyperthyroidism can be complicated by addisonian hyperpigmentation, and vitiligo develops in about 7% of thyrotoxic individuals.[38]

Hyperpigmentation resembling chloasma, pellagra, and Addison disease is uncommon in post-thyroidectomy hypoparathyroidism. Hyperpigmentation and vitiligo may be present in the idiopathic hypoparathyroidism.[38]

Phototoxic and photoallergic reaction

A review of medication use, supplement use, and exposure to plants and ultraviolet radiation can help determine whether hyperpigmentation is caused by a medication adverse effect or a phototoxic reaction.[47]

Diffuse inflammation followed by hyperpigmentation in sun-exposed areas may be observed in any age without being hormone related, resulting from a combination of sun exposure and an offending medication, plant, or chemical.

Many medications, such as amiodarone, amitriptyline, bleomycin, clofazimine, cyclophosphamide, minocycline, phenothiazines, and zidovudine, among others, may induce hyperpigmentation.[51]

Internal malignancies

Malignant acanthosis nigricans may present before, after, or concurrent with the diagnosis of malignancy that may be intraabdominal adenocarcinoma, most strongly gastric carcinoma; lung, liver, uterus, breast, or ovary carcinoma; and lymphoma or mycosis fungoides.[60]

The ectopic adrenocorticotrophic hormone–producing syndrome presents as Cushing syndrome, edema, proximal muscle weakness, mental confusion, diabetes mellitus, hypertension, and intense hyperpigmentation. Oat cell carcinoma is the most commonly associated tumor; but other cancers are also associated, such as pancreatic islet cells, thyroid, parotid, ovary, testes, colon, gallbladder, breast, bronchial, biliary tract, and others.[37,59]

In Peutz-Jeghers syndrome, frecklelike lesions on the lips, nose, buccal mucosa, fingertips, and under the nails are

present. Perioral pigmentation is typical. The development of cancer is relatively uncommon, but association with neoplastic complications has been reported.[37]

Neurocutaneous disorders

Neurofibromatosis consists of 8 distinct forms, and the first 2 are the most common. Both forms present café au lait macules greater than 5 mm in prepubertal patients and greater than 15 mm in postpubertal patients.[61]

Tuberous sclerosis complex is the second most common neurocutaneous disorder. The earliest detectable abnormalities are hypomelanotic macules, which are seen in at least 90% of affected patients.[61]

POEMS syndrome is an uncommon multisystem disorder characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes. The most common skin finding is diffuse hyperpigmentation, which occurs in more than 90% of patients.[61]

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