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

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Abstract White diseases are a heterogenous group characterized by hypopigmentation or depigmentation. Skin and eye color are determined by the number and size of melanosomes present. Melanin is produced by melanosomes in the melanocytes present within the epidermis of the skin, uvea, and retinal pigmented epithelium (RPE). Conditions altering the number of melanocytes or concentration of melanin result in a lack of pigmentation, appearing as "white diseases" ranging from the well-known albinism and vitiligo to more esoteric white hand syndrome and Degos disease.

Introduction

Disorders of hypopigmentation and depigmentation comprise a large group of conditions that are characterized by altered melanocyte density or melanin concentration. Conditions may be inherited, such as albinism, piebaldism, or Waardenburg syndrome; others, like tinea versicolor, lichen sclerosus, and intralesional steroid injection-related hypopigmentation, are acquired. Some conditions may masquerade as depigmentation disorders by producing scale, appearing as rough, white skin that is dry and cracked. This represents the loss of the outer layer of the epidermis rather than a disorder of depigmentation and is typically secondary to other skin conditions.

Albinism

Definition

Albinism is defined as generalized cutaneous hypopigmentation compared with others of the same ethnicity that is due to aberrant melanin production.[1] The most common form of albinism also causes significant ocular effects and is, therefore, named oculocutaneous albinism (OCA). This disease affects 1 in 20,000 individuals across the world and is seen across all ethnicities.[2] There are four subtypes (OCA1-4), each with its own unique characteristics, with OCA-1 and OCA-2 being the most common. If the characteristic ocular findings are present and there are no signs of skin

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or hair hypopigmentation, the disorder is termed ocular albinism (OA).[1]

Etiology and pathogenesis

OCA is inherited in an autosomal recessive fashion, leading to a deficiency of the enzymes needed to produce melanin.[1] The most severe form of albinism is OCA1A, in which there is no tyrosinase (TYR) activity.[3] The rate-limiting step of melanin synthesis involves converting tyrosine to L-dihydroxyphenylalanine (DOPA) and then into dopaquinone, which is performed by TYR.[3] Mutations that leave residual TYR activity result in OCA1B, which allows for some level of pigment accumulation throughout a lifetime.[3] There is also a rare temperature sensitive variant of OCA1, in which TYR is inactivated at 37°C or above.[2]

In OCA2, mutations in the *OCA2* gene leads to abnormal biogenesis of melanosomes and abnormal transporting of TYR to the melanosome.[4] The pathophysiology of OCA3 involves mutations leading to abnormal formation of tyrosinase-related protein1, thus disrupting the melanin-synthesis pathway.[2] OCA4 is caused by mutations of membrane-associated transporter protein, of which the function is still unknown.[3]

With regards to the ocular effects, reduction of melanin causes incomplete development of the fovea normally induced by the RPE, in addition to changes in the routing of axons within the optic nerves.[4] Macular hypoplasia causes the most significant vision impairment in individuals with OCA.[1] Misalignment of optic nerve axons can lead to excessive crossing of the fibers at the optic chiasm causing strabismus, which is commonly seen in OCA.[3]

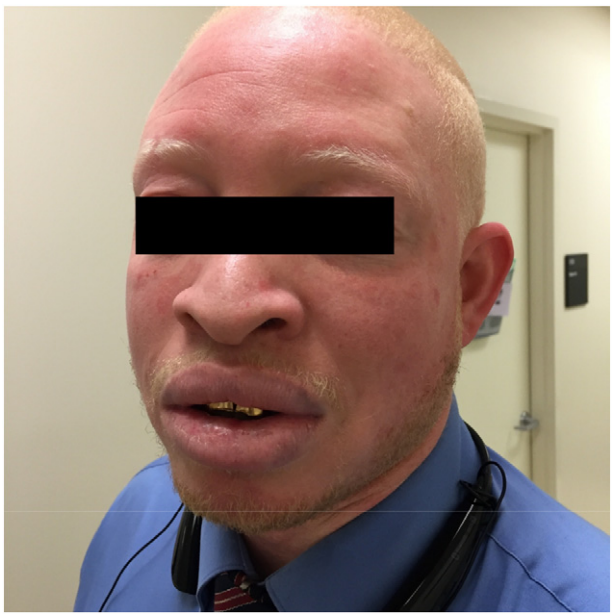

Fig. 1 Oculocutaneous albinism type 2.

Clinical and histologic manifestations

Individuals with OCA1 will have white eyebrows, eyelashes, and hair with no accumulation of pigment over time.[3] The irises are translucent and appear pink or light blue.[3] The temperature sensitive variant of OCA1 causes hypopigmentation in areas, where the body is warmer, resulting in white hair only on the scalp, axilla, and genital area.[2]

In OCA1B and OCA2, the amount of pigment varies within the skin and irises, and OCA2 newborns almost always have color within the hair (Figure 1).[3] OCA3 is also known as Rufous OCA, and is seen in African individuals, where it produces a red tint to the skin and red hair.[3] OCA4 cannot be distinguished clinically from OCA2.[3]

All subtypes of OCA have similar ophthalmologic findings when compared OA. This includes various degrees of nystagmus, strabismus, hypopigmentation of iris, reduced pigment in the RPE, foveal hypoplasia, and reduced visual acuity.[3]

Differential diagnosis

Other causes of generalized hypopigmentation should be differentiated from OCA. These diseases are associated with additional systemic manifestations and are termed syndromes of albinism:

- Hermansky-Pudlak syndrome: characterized by hypopigmentation, optic deficits as seen with OCA, platelet dysfunction leading to bleeding events, and ceroid accumulation in lysosomes.[5] Hermansky-Pudlak syndrome is rarer than OCA and most commonly seen in the Puerto Rican population.[5] Interstitial lung fibrosis, inflammatory bowel disease, and bleeding events are possible results of the disease process.[1,5]
- Chediak-Higashi syndrome: characterized by hypopigmentation, prolonged bleeding times, decreased natural killer cell function, and peripheral neuropathy.[5] This disease can lead to death from decreased defenses to bacterial infection or from lymphoproliferation within major organs.[5]
- Griscelli syndrome: characterized by hypopigmentation and silver hair, large aggregates of pigment within hair shafts, and accumulation of melanosomes within melanocytes.[5] Immune impairment as well as neurologic deficits are possible depending on the genetic variant inherited.[5]
- Cross-McKusick-Breen syndrome: characterized by cutaneous and ocular hypopigmentation, mental retardation, and motor deficits.[5] This a rare disease with a broad clinical spectrum. Most cases are reported in siblings which are the result of a consanguineous marriage.[5]
- Waardenburg syndrome, type 2: characterized by OA as well as sensorineural deafness.[3]
- X-linked recessive OA: due to mutations in a protein responsible for controlling melanosome quantity and size rather than decreased melanin synthesis.[1] Lyonization can lead to clinical findings in the female carrier.[5]

Laboratory studies

Clinical overlap between the OCA subtypes makes them difficult to distinguish; thus, molecular diagnosis may be needed if differentiation is desired.[3] Molecular genetic testing of *TYR* and *OCA2* genes are available for the diagnosis of OCA-1 and OCA-2 respectively.[3] However, genetic confirmation is generally not desired and does not change the course of clinical treatment.[4]

Treatment

Individuals with OCA do not have a limited lifespan or further medical problems outside of the ocular and cutaneous manifestations[3]; however, melanin normally absorbs ultraviolet radiation and reduces radiation induced DNA damage of the skin.[4] Protection from the sun, daily use of sunscreen, and regular full body skin checks are highly recommended for these patients. The visual deficits often require that the individual wears glasses, and photophobia can be ameliorated with dark lenses. Despite this, their vision will likely remain limited due to macular hypoplasia.[1] Although there are no pharmacologic treatments available for albinism, the ongoing research is directed toward agents that increase L-DOPA and tyrosine, thus supplementing the melanin-synthesis pathway.[4]

Degos disease (malignant atrophic papulosis)

Definition

Degos disease, also known as malignant atrophic papulosis and described by Robert Degos (1904-1987) in 1942, is a rare disease of unknown etiology. It has been reported less than 200 times in the current literature.[6] This illness portends a variable prognosis dependent on whether it is localized to the skin, where many consider it to be "benign" versus systemic involvement.[6] Systemic disease involves lesions of the gastrointestinal (GI) tract and central nervous system with a fatal prognosis. Degos disease involves pathognomonic skin lesions of erythematous papules that later develop porcelain-white centers.[6]

Etiology and pathogenesis

The etiology of Degos disease remains a mystery. There are multiple hypotheses which include vasculitis, coagulopathy, viral infection, and endothelial cell dysfunction.[7] No matter the organ involvement, Degos disease consistently causes vascular damage with secondary thrombosis and tissue necrosis.[8] It is postulated that Degos disease is not a disease, but a pattern expressed due to other connective tissue diseases. There is support for this hypothesis with relation to systemic lupus erythematosus (SLE) in particular, as the histologic findings of Degos disease are often indistinguishable from SLE[8]; however, others oppose this theory through emphasis of Degos disease's resistance to treatment, lack of consistent laboratory findings or autoantibodies, and absence of the photosensitive facial eruption of typical SLE.[9]

Degos disease has not been proven to be an inherited disorder; however, there exist several reports of familial occurrences. One case involves six affected family members spanning across three generations.[10] There have been other reports of familial cases spanning across multiple generations, leading to suspicions of autosomal dominant or X-linked dominant inheritance.[10]

Clinical and histologic manifestations

Cutaneous findings of Degos disease are consistent between localized and systemic disease. The lesions start as erythematous papules ranging from 2 to 15 mm in diameter and then progress within a few weeks to form an umbilical "porcelain-white" scar with a surrounding telangiectatic rim.[7–9,11] The papules are usually numerous and primarily involve the trunk with sparing of the face, palms, and soles.[9] The mucous membrane most affected is the eye, of which the most common lesion is an avascular patch of the conjunctivae.[8] The lesions may be associated with burning sensation but are otherwise asymptomatic.[9]

Systemic Degos disease develops after the presentation of cutaneous findings, but the time of systemic onset ranges from weeks to years from the first cutaneous lesion.[9] Internal organs are usually affected via infarction.[6,8] Greater than 50% will have involvement of the GI tract, and 20% will have central nervous system involvement.[9]

Biopsy shows several variable findings on histology. As the lesion progresses through its predictable sequence from erythematous papule to porcelain-white scar, the histology transforms as well. Early papules display superficial and deep perivascular, perineural and periadnexal lymphocyte infiltration, in addition to interstitial mucin deposition.[11] In a mature papule, the central white area will demonstrate prominent interface reactions showing squamatization of the dermoepidermal junction, epidermal atrophy, melanin incontinence, and papillary dermal sclerosis.[9,11] It has been noted that the early stages histologically resemble tumid lupus erythematous, whereas the porcelain-white scar resembles lichen sclerosus et atrophicus.[7,9,11] One of most characteristic findings includes wedge-shaped connective tissue degeneration and necrosis, which correlates with thrombotic occlusion leading to tissue infarction.[7,9]

Differential diagnosis

The differential diagnosis of Degos disease includes atrophie blanche, connective tissue disease, dermal mucinosis, guttate lichen sclerosus, and guttate morphea.[9] Degos disease is rare and thus a diagnosis of exclusion. In systemic disease,

other causes of GI bleeding and neurologic injury must be investigated first.

Laboratory studies

Anemia may be a sign of intestinal bleeding and should be investigated further if skin lesions are present; however, there are no laboratory tests that indicate a diagnosis of Degos disease.[7,9]

Treatment

There have been no reports of consistent responses to antiplatelet therapies, corticosteroids, or immunologic therapies.[10]

Prognosis

Prognosis of Degos disease is dependent on whether there is systemic involvement. Once an individual has invasion of the internal organs, death is predicted within 2 to 3 years.[9] The most common cause of mortality is intestinal perforation.[9] Pure cutaneous Degos disease does not affect the lifespan; yet, systemic involvement may develop at any time, sometimes years after cutaneous lesions appear. This makes it imperative that frequent medical followup occurs to rule out systemic disease.[7]

Halo nevus of Sutton

Definition

A halo nevus (HN), first described by Richard Sutton, Sr, (1879-1952) in 1916 as leukoderma acquisitum, is a melanocytic nevus that develops a surrounding border of depigmentation.[12] This progresses to regression and involution of the nevus altogether with a process that can take many years to complete. Most cases of HN are reported in conjunction with acquired benign melanocytic nevi, though the phenomenon can also be associated with congenital nevi, basal cell carcinomas, and melanomas.[12]

Etiology and pathogenesis

The incidence of HN is 1% of the population and usually arises in adolescence, although it can occur at any age.[12,13] The underlying etiology of HN has not yet been fully elucidated; however, most researchers have come to the consensus that the process is immune mediated with involvement of CD8+ T cells.[13–16] The abundance of CD8+ T cells and increased Langerhans cells present upon histologic examination supports the hypothesis of an autoimmune process.[16]

Vitiligo-like skin lesions commonly develop either simultaneously with HN or shortly after, supporting the hypothesis that HN is due to loss of self-tolerance toward melanocytes.[15] The inciting event leading to melanocyte destruction has not yet been discovered; however, it is hypothesized that HN may be a stage of early melanoma rejection.[14]

Clinical and histologic manifestations

The clinical appearance of HN includes melanocytic nevi with a perimeter of depigmentation (Figure 2). The most common location on the body is the trunk, with particular propensity for the back.[12,13,15] It is more commonplace for patients to have multiple HN rather than one singular lesion.[13] The appearance of the halo marks the beginning of nevus regression.[15] Eventually, the halo will disappear as well, but the timeline of resolution is variable, spanning from only 1 month to upwards of a decade.[12]

Histologic examination of halo nevi is more likely to show an increased number of Langerhans cells, as well as increased lymphocytic infiltrate versus a nevus without halo[15]; however, the extent of these changes depends on which stage the lesion is in at the time of biopsy. The melanocytic portions of HN undergo four stages as they involute and regress. In the first stage, nests of nevus cells are encompassed by a moderate number of lymphocytes. During the second stage, there are increased numbers of lymphocytes as well as Langerhans cells, and the

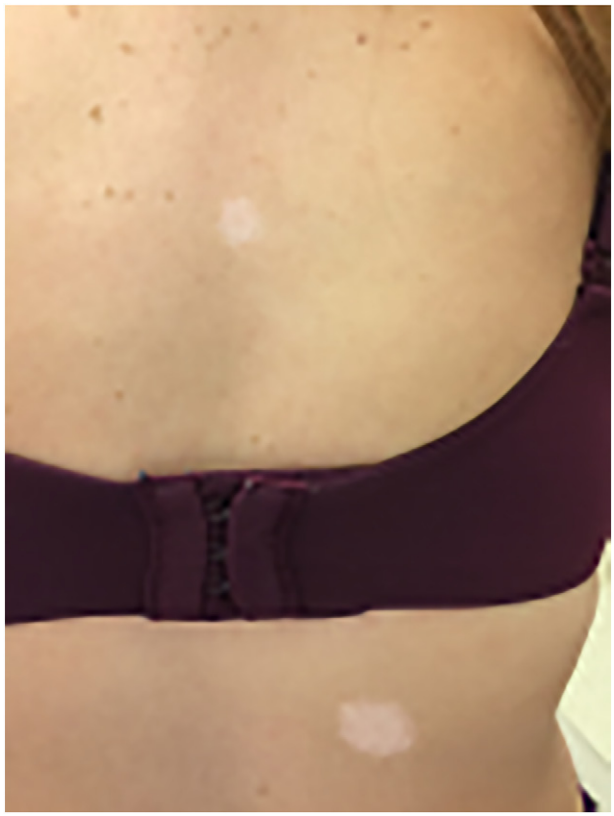

Fig. 2 Halo nevi.

nests of nevus cells begin to have ragged edges. Stage three is the late regression phase and is characterized by disconnected nevus cells with mild atypia in addition to persistent lymphocyte invasion as well as increased numbers of Langerhans cells. At stage four, complete regression has occurred and there are no remaining nevus cells, although a moderate amount of lymphocytes linger.[16]

Differential diagnosis

Melanoma must be at the top of the differential, as it is possible the pigment change typical of HN could be a result of malignant transformation[12]; however, it is expected that the halo would be more irregular in the case of melanoma.[13] The differential may also include vitiligo. There is debate regarding the many reported cases of association between HN and vitiligo. Some argue that the depigmentation of distal areas commonly observed with HN is actually halo nevi-associated leukoderma, which is nonsymmetrical and mild in comparison to vitiligo.[15]

Treatment and prognosis

Most cases of halo nevi are benign, and only short-term followup is necessary to monitor for potential malignant changes.[13]

Idiopathic guttate hypomelanosis

Definition

Idiopathic guttate hypomelanosis (IGH) is characterized by diffuse hypopigmented macules, typically between 1 to 3 mm in diameter, on sun-exposed areas of the body.[17]

Etiology and pathogenesis

The condition most commonly affects fair-skinned individuals and is related to sun exposure and age but may also be seen in darker skin patients. IGH can run in families indicating a genetic component to its pathogenesis.[18] In one study, those who use "body scrubbers" were more likely to have IGH lesions suggesting a relation to repeated microtrauma over extended periods of time; however, details about the condition's pathogenesis remain unclear.[17]

Clinical and histologic manifestations

IGH presents as hypopigmented macules, 1 to 3 mm in diameter, diffusely located in sun-exposed areas such as the face, back, and extremities (Figure 3). Lesions are otherwise asymptomatic. In contrast to vitiligo, IGH macules do not typically grow or coalesce to cover large areas.

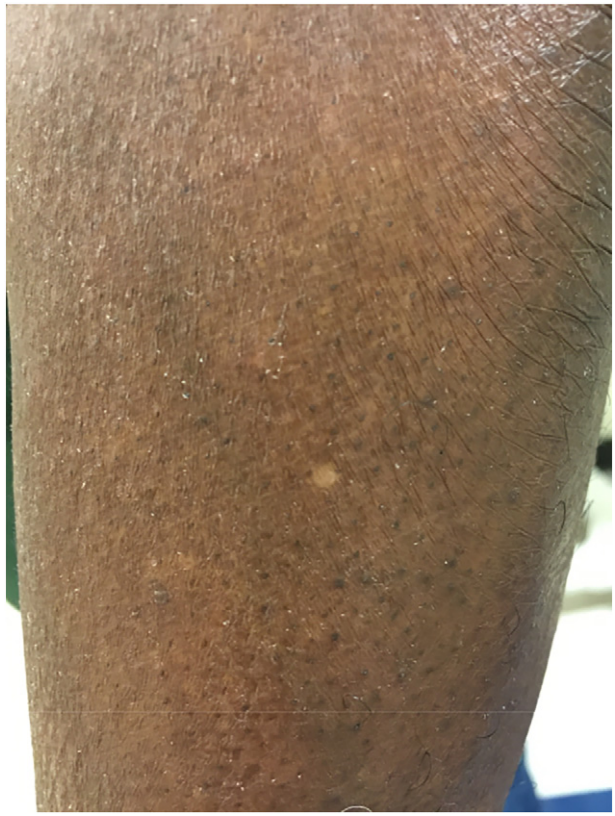

Fig. 3 Idiopathic guttate hypomelanosis.

Under histologic examination, the lesions of IGH show decreased melanin content and reduced numbers of melanocytes. In addition, hyperkeratosis, an atrophic epidermis, and flattened rete ridges can be present.[19]

Differential diagnosis

The differential diagnosis includes pityriasis alba, tinea versicolor, hypopigmented flat warts, and vitiligo. Eliciting the progression of the disease, age of onset, family history, distribution of the macules, and size of the macules can help delineate IGH from other hypomelanotic diseases. Given the patient's history and environmental exposures, it may be important to consider other rarer causes of hypomelanosis such as arsenic exposure.[20]

Treatment

Although IGH is benign, patients often seek treatment. Patients should be encouraged to wear sunscreen when outdoors and avoid artificial tanning beds. If additional treatment is desired, effective therapeutic regimens include fractional photothermolysis, excimer laser, phenol, topical 0.1% tretinoin, and cryotherapy.[21–25] A single cryotherapy session has been shown to produce clinically significant repigmentation at 4 months[22]; however, cryotherapy in subjects with dark-colored

skin should be performed with caution due to the high-risk for surrounding dyspigmentation. Microinfusion of 5-fluorouracil into IGH macules using a professional tattoo machine has effectively induced pigmentation.[26]

Prognosis

Lesions are benign, typically do not progress nor repigment significantly. More lesions are likely to appear with age.[17]

Intralesional steroid injection

Definition

Intralesional steroid injections are used in the treatment of a wide variety of conditions. A rare, yet important side effect, involves hypopigmentation of the skin surrounding the injection site. Whether triamcinolone acetonide 40 mg/mL or 10 mg/mL is used, hypopigmentation can occur.

Etiology and pathogenesis

The exact mechanism by which steroids reduce pigmentation is unknown. Studies report that melanocytes in the affected area are intact, so it has been theorized that steroids impair the function of these cells.[27,28]

Clinical and histologic manifestations

Reduced pigment near an injection site appears within a few weeks (Figure 4). Both linear and branch-like patterns have been reported.[27–30] A lymphatic mechanism of drug spread to nearby tissues has been suggested given the branch-like pattern of some cases.[28,31] Another case report described a serpiginous pattern of hypopigmentation indicative of superficial venous spread.[32] Hypopigmentation may or may not be associated with subcutaneous atrophy.[31]

Differential diagnosis

Intralesional steroid injection induced hypomelanosis can usually be identified due to its chronologic relationship to a steroid injection. If the onset of hypomelanosis occur before the injection, several months after the injection, or change significantly outside of few weeks from the injection, this should prompt evaluation for a different etiology.

Treatment and prognosis

There is no specific treatment for this condition. In many cases, hypopigmentation will resolve or partially resolve after several months of stopping steroid injections[31,32]; however, some patients have permanent hypopigmentation even after many months.[33]

Lichen sclerosus

Definition

Lichen sclerosus (LS) is characterized by porcelain-white papules and plaques that classically involves the skin of the vulva and perianal region of postmenopausal women; however, men and children can also be affected.[34]

Etiology and pathogenesis

The cause of LS is unknown. In women, there is an increased incidence of tissue-specific antibodies and associations with other autoimmune diseases, especially thyroid disease, suggesting an autoimmune mechanism for LS.[35–38] These associations are not seen in men but rather with tobacco use, coronary artery disease, diabetes mellitus, and increased body mass index.[39–41] Additionally, an association of LS with urostomy, hypospadias, and ileostomy suggests that moisture and irritation may play a role in the etiology of LS.[42] Trauma predisposes to LS; lesions may appear in surgical wounds, following radiotherapy, and after sunburn.[43–46] Finally, there are genetic associations with human leukocyte antigen class II antigens.[47–50]

Clinical and histologic manifestations

In general, the typical lesions are porcelain-white papules and plaques.[34] Female anogenital is the most common variant and is characterized by lesions in the interlabial sulci, labia minora, clitoral hood, clitoris, and perineal body (Figure 5). Notably, the vaginal mucosa and cervix are not involved. Patients will often report itching that is worse at night. The disease may progress to form fissures and erosions, which present with pain and dyspareunia.[34]

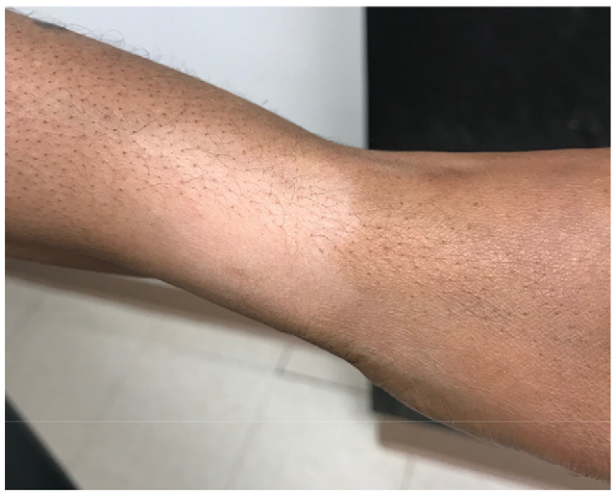

Fig. 4 Intralesional corticosteroid injection-related hypopigmentation.

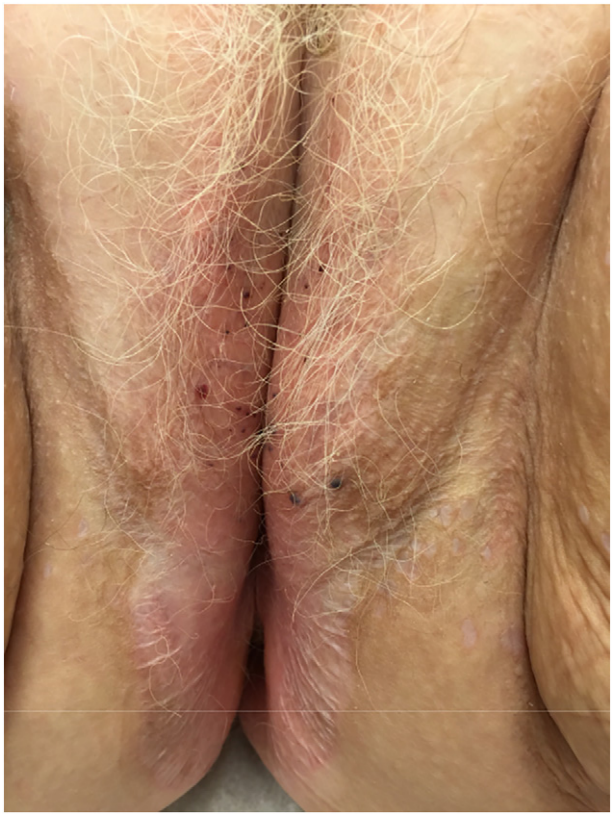

Fig. 5 Lichen sclerosus.

The anogenital variant in girls resembles that of women but has a notable potential for marked ecchymosis. This may lead to suspicions of child abuse. It is important to rule abuse out as an aggravating factor, as LS may present secondary to trauma.[51,52]

In men, lesions present on the prepuce, coronal sulcus, glans penis, or on the shaft of the penis. Patients may describe tightening of the foreskin, painful erections, dysuria, and poor urinary stream in addition to the appearance of lesions. Men are more likely to experience clinical manifestations and describe soreness or decreased sensitivity over the area.

In boys, the development of phimosis is a concern, as the prepuce is commonly involved. In contrast to other presentations, the perianal skin is rarely involved. Extragenital manifestation can classically occur in the upper part of the trunk, axillae, buttocks, lateral aspect of the thighs, and rarely the face and scalp.[34]

Histologically, LS is characterized by a vacuolar interface reaction pattern in conjunction with homogenized and hyalinized collagen bundles intervening between inflammatory infiltrate, epithelium, or vessel walls. In early stages, epidermal findings may be located around adnexal structures with acanthosis, hypergranulosis, and dystrophic hair. In the dermis, early changes include homogenized collagen and widened capillaries.[53]

Differential diagnosis

LS may be distinguished from lichen planus and psoriasis, both of which can mimic LS in appearance. This can often be done clinically, though a biopsy may be indicated in some patients. Clinical clues suggesting lichen planus include involvement of the vagina and cervix, which are rarely involved in LS. Other diseases to be considered are mucous membrane pemphigoid, genital psoriasis, herpes simplex virus infection, and candidiasis.[34]

Laboratory studies

Swabs are not required routinely but may be indicated in erosive or topical steroid-resistant disease to exclude herpes simplex virus or *Candida albicans* as additional complicating problems. Screening for autoimmune diseases may be indicated based on clinical suspicion.[34]

Treatment

When discussing treatment for LS, an urgent referral to urology is indicated, if squamous cell carcinoma (SCC) is suspected at any stage. If not confident of clinical diagnosis or not experienced in management of LS, the patient should not be treated empirically with a potent steroid and consider a confirmatory biopsy. If the diagnosis is certain, treatment may be initiated with clobetasol propionate 0.05% ointment 3-month induction regiment. The suggested regimen is once daily application for 1 month, alternate days for 1 month, and finally twice weekly for 1 month. In addition, soap substitution, emollients, and avoidance of irritants are recommended.

Assess response at 3 months including sexual function. If treatment was unsuccessful, check compliance, reconsider diagnosis, check for change of clinical manifestations suggesting vulvodynia or urinary incontinence, and continue topical steroids once or twice weekly. If clinical manifestations persist, consider referral to a specialist for psychosexual issues or surgical intervention for recurrent fissuring, release of adhesions in women, or circumcision in men.

Intralesional triamcinolone may be considered in women with LS with topical steroid-resistant, hyperkeratotic areas after intraepithelial neoplasia or malignancy has been excluded by biopsy. Other considerations include the use of tacrolimus and pimecrolimus.[34]

Prognosis

There is generally a good prognosis for acute genital cases of LS; however, one of the most feared complication of untreated LS is SCC. Although only a 5% lifelong risk, there does appear to be correlation with LS and SCCs.[54–56] Scarring is another important complication of LS. In women, introital narrowing can occur leading to dyspareunia and difficulties micturating.[34] Surgery may need to be considered if severe

enough.[57] Other complications include phimosis and painful erections in men, dysesthesia in genital area, and psychosexual problems.[34]

Lichen striatus

Definition

Lichen striatus (LStr) is the most commonly acquired, self-limiting, unilateral linear dermatosis following Blaschko lines that resolves spontaneously. It is most frequently seen in children aged 4 to 6 months to 15 years with a female predilection; the mean age of diagnosis is 3 years, and the duration of disease is 9.5 months.[58,59] The eruption is characterized by a pink eruption that coalesces to form a linear band along Blaschko lines most commonly found on the extremities and rarely effects the nail matrix.[58]

Etiology and pathogenesis

The etiology of LStr is unknown, but it may be precipitated by infective agents, cutaneous injury, trauma, and hypersensitivity.[59] Additionally, the presences of atopy has been theorized to be a contributing factor, with the abnormal immune status of the patients acting as a predisposing factor; however, the presence of atopy has no effect on onset, extension, or duration of disease.[59]

The pathology can be viewed as a consequence of a stimulus that induces a predisposed environment leading to the loss of immunologic tolerance to embryonically abnormal keratinocytic clones. This leads to a T-cell mediated inflammatory response which is characterized by epidermal infiltration by CD8+ T lymphocytes surrounding necrotic keratinocytes and activated Langerhans cells. In the pediatric population, this reaction can be very strong, leading to deletion of the mutant clones, which then precludes relapse.

Clinical and histologic manifestations

LStr exists in three distinct clinical patterns: (1) typical LStr, (2) LStr albus, and (3) nail LStr.[59]

Typical lichen striatus presents as pink, red or flesh-color, flat topped papules sometimes with scaly surfaces (Figure 6). Lichen striatus albus exhibits hypopigmented macules or papules with only a few typical lichenoid pink papules. Nail LStr includes onychodystrophy, thinning, longitudinal ridging and splitting, fraying and onycholysis restricted to the lateral portion of the affected nail, or more rarely to the medial portion.[59]

The histologic features of LStr include focally band-like lymphocytic infiltrates with variable exocytosis and collections of histiocytes in the dermal papillae.[60] There is also alignment of the infiltrate with hair follicles and eccrine ducts and intraepithelial vesicles filled with Langerhans cells and CD8+ lymphocytes. Other features include mild spongiosis with exocytosis, hyperkeratosis, and parakeratosis with a few necrotic keratinocytes in the epidermis.[61]

Differential diagnosis

Additional linear dermatoses that follow Blaschko lines can mimic lichen striatus. Many early lesions can resemble linear morphea, however mature lesions show epidermal atrophy, sclerosis, and dermal fibrosis.[62] Inflammatory linear verrucous epidermal nevus, Blaschkitis, and linear cutaneous lupus erythematosus lack spontaneous regression and thus are differentiated from LStr.

Treatment

LStr is self-limiting and spontaneously regresses, thus no treatment is necessary. Topical steroids do not affect the dura-

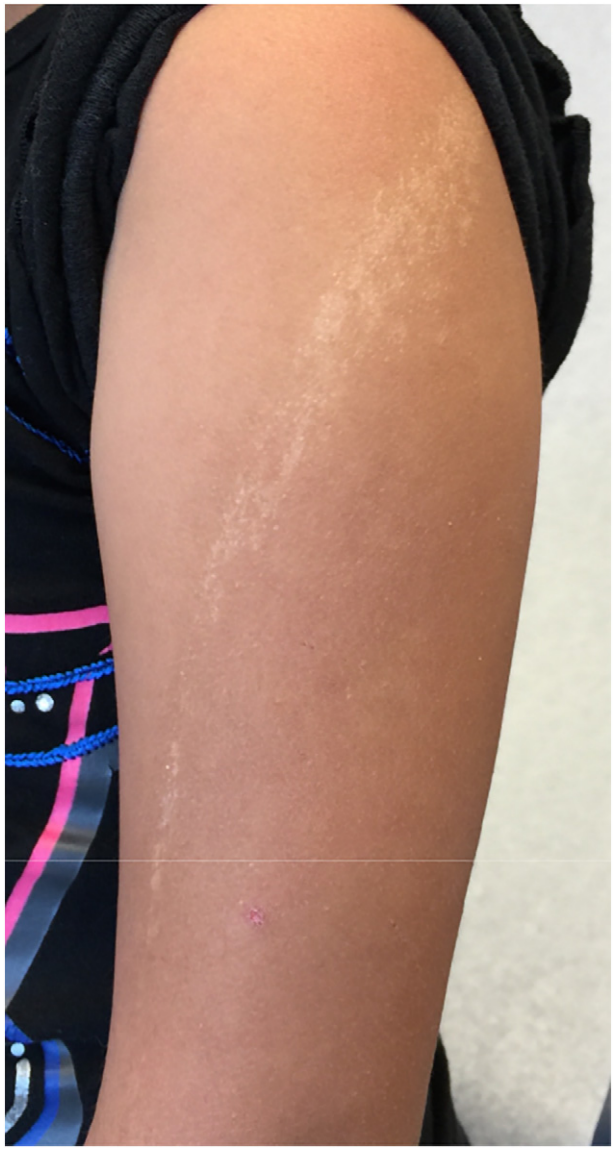

Fig. 6 Lichen striatus.

tion of the disease or the postinflammatory hypopigmentation.[59] Tacrolimus and pimecrolimus have been beneficial in some recalcitrant and relapsing cases.[63]

Prognosis

The eruption is benign and spontaneously resolves without scarring within months. It may leave behind transient hypopigmentation that can last up to several years.[59]

Piebaldism

Definition

Piebaldism is a hypopigmentation disorder characterized by congenital onset white forelock and symmetrical leukoderma involving the scalp, forehead, abdomen, and knees.[64] It is primarily caused by mutations of the c-Kit proto-oncogene, resulting in a congenital absence of melanocytes.

Etiology and pathogenesis

Manifestations of piebaldism occur secondary to *KIT* gene mutations. Mutations are inherited in an autosomal dominant fashion. The *KIT* gene encodes a type III transmembrane receptor tyrosine kinase which binds stem cell growth factor onto melanocytes.[65] The KIT ligand and KIT interaction has downstream functions essential to the migration, proliferation, survival, melanogenesis and melanosome transfer of melanocytes.[64,66] Loss of most or all melanocytes in depigmented areas is a result of a lack of melanoblast migration during embryogenesis.

Genetic analysis has suggested a genotype-phenotype correlation in piebaldism with more severe mutations resulting in more pronounced disease; however, other factors such as modifier gene *MC1R* can also contribute to severity of disease.[64] Severe phenotypes have been associated with dominant negative inhibition caused by a missense mutation in the tyrosine kinase domain of c-Kit.[64]

Mutations in the *SNAI2* gene, encoding a zinc-finger neural crest transcription factor, have been found in patients who lack *KIT* gene mutations. The gene product mediates a signaling pathway important in melanoblasts development.[67] Heterozygous mutations are thought to lead to piebaldism whereas homozygous mutations are associated with Waardenburg syndrome.[68]

Clinical and histologic characteristics

Clinically piebaldism appears as well-defined depigmented patches of skin and hair most commonly affecting the frontal scalp, forehead, abdomen, and extremities in a symmetrical distribution (Figure 7). Due to the nature of the pathogenesis, the lesions are present at birth and stable throughout life. Small hypopigmented macules (1-1.5 cm) can be acquired over time and are frequently observed surrounding the achromic areas.[65] Disease severity depends on locus of c-Kit mutation. Mild disease may be characterized by an isolated white forelock.

Histologically, melanocytes are absent or severely diminished in depigmented areas but normal in surrounding pigmented areas.[66]

Differential diagnosis

The differential diagnosis includes other disorders of depigmentation, including Waardenburg syndrome, vitiligo, nevus depigmentosus, OCA, pigmentary mosaicism, and neurofibromatosis type 1 (NF1). Waardenburg has piebaldlike leukoderma and forelock however it also possesses pigmentary changes of the iris, sensorineural hearing loss, and various other abnormalities such as musculoskeletal problems or Hirschsprung disease in certain variants.[64] Vitiligo has a progressive course of leukoderma in the skin, mucosa, and hair; piebaldism has stable leukoderma. Like piebaldism, nevus depigmentosus is present at birth but can be differentiated based on clinical picture. Nevus depigmentosus has irregular serrated borders and exist in singular, segmental, and systematized form and is typically unilateral as compare to symmetrical seen in piebaldism. NF1 is included in the differential because multiple café au lait spots are seen in piebaldism. When other features of NF1 are present in the face of piebaldism, genetic testing should be performed to evaluate coexistence.[64]

Treatment and prognosis

Piebaldism represents a medically benign phenotype. Leukoderma is stable throughout life; however, there are some

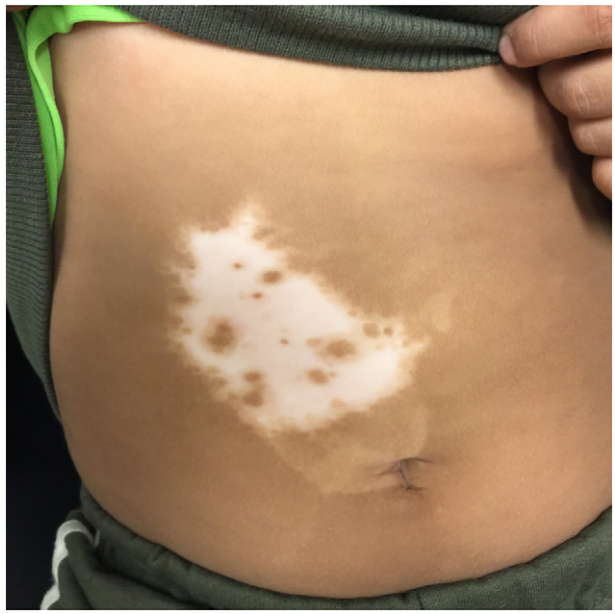

Fig. 7 Piebaldism.

cases of spontaneous partial repigmentation in children.[65] Options for patients include cosmetic camouflage, artificial pigmentation with dihydroxyacetone, and grafting. Grafting may be done through suction blister epidermal grafting, autologous punch grafting, noncultured epidermal cellular grafting, cultured epidermal autografts, and combination neodymium-doped: yttrium-aluminum-garnet laser treatment with autologous cultured epidermis grafting.[64] These surgical trials have had varying success with autologous transplantation of melanocytes reaching 100% repigmentation.[66]

Pityriasis alba

Definition

Pityriasis alba (PA) is a benign dermatitis characterized by round to oval hypopigmented macules or plaques found on the face, upper portions of the trunk, and upper extremities. It is commonly found in children and adolescents and more apparent in darker skin tones.

Etiology and pathogenesis

There is currently no known etiology for PA but it has been linked to unprotected sun exposure, poor hygienic habits, and cutaneous signs of atopy.[69] Other risk factors include young age and darker skin.[70] The use of long or frequent baths, mechanical exfoliants, and other harsh skin treatments have also been shown to increase the frequency of PA. It is postulated these activities remove normal epidermal defensins and other skin protective substances, thus increasing the susceptibility to developing PA. Additionally, low levels of copper have also been shown to correlate to the etiology of PA. Copper is required to activate tyrosinase in melanocytes.[71]

Clinical and histologic manifestations

PA presents as an asymptomatic or mildly pruritic round to oval hypopigmented lesion most commonly on the face and more apparent on sun-exposed areas (Figure 8). The lesions contain indistinct margins and are often associated with scaling and erythema.[72]

Histologically, the lesions are characterized by a decrease in melanin and a variable amount of melanocytes.[73] The lesions may also demonstrate perivascular lymphocytic infiltrates, spongiosis with exocytosis, hyperkeratosis, and acanthosis.

Differential diagnosis

The differential diagnosis includes postinflammatory hypopigmented lesions, vitiligo, fungal infections, and hypopigmented mycosis fungoides. Vitiligo can be differentiated by fluorescence on woods lamp with sharply demarcated edges;

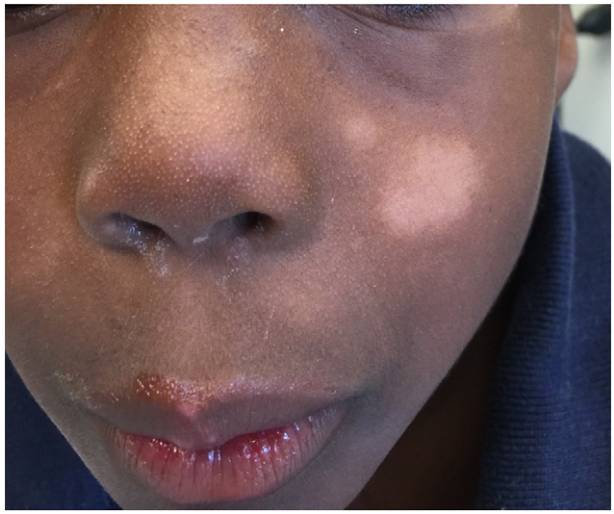

Fig. 8 Pityriasis alba.

PA has indistinct margins and does not fluoresce. Fungal infections can be ruled out via potassium hydroxide preparation. Biopsy allows for the differentiation from mycosis fungoides. Leprosy, ash-leaf macules of tuberous sclerosis, and hypopigmentation from topical medications should also be considered.[72]

Treatment

Low-potency corticosteroids can be used to accelerate repigmentation and reduce the associated pruritus and erythema. The dosages used include 0.5% and 1% hydrocortisone cream or ointment and diiodohydroxyquinoline until resolution of lesion and associated clinical manifestations.[70,72] One study used 0.1% tacrolimus ointment to reduce hypopigmentation, pruritus, and scaling and concluded that it may be used as an alternative to corticosteroids for facial lesions.[74] Other treatments include emollients for the scaling and sunscreen to prevent darkening of surrounding skin.

Prognosis

The disease is benign and self-limited. Patches and plaques will resolve between several months to a few years.

Pityriasis lichenoides chronica

Definition

Pityriasis lichenoides chronica (PLC) is part of a rare, benign, inflammatory skin spectrum disorder with pityriasis lichenoides encompassing all: PLC, pityriasis lichenoides et varioliformis acuta, which is also known as Mucha-Habermann disease, and febrile ulceronecrotic Mucha-Habermann

disease.[75] The disorder initially presents as papules with a red-brown hue and develop a micalike scale. The papules can spontaneously flatten and regress and leave behind areas of hyperpigmentation or hypopigmentation. The lesions can last for several weeks and the entire course of eruptions can take many years.

Etiology and pathogenesis

The exact pathogenesis of PLC is currently unknown.[76] Theories regarding the pathogenesis include an inflammatory reaction triggered by an infectious agent, an inflammatory reaction in response to T-cell dyscrasia, and an immune-complex mediated hypersensitivity vasculitis.[75] Infectious exposures have been studied in *Toxoplasmosis gondii*, Epstein-Barr virus, HIV, parvovirus B19, and cytomegalovirus; young age of exposure and familial outbreaks also support the infectious etiology. Lymphoproliferative theory stems from monoclonality detected in the CD4+ T cells of PLC.

Clinical and histologic manifestations

PLC develops as monomorphic red-brown papules with an overlying mica scale that are present at all stages of development. The papules progress over weeks to months and follow a relapsing-remitting course. The trunk and arms are the most common areas affected. When they disappear an area of hyper or hypopigmentation without scarring is left behind which is more prominent in darker skin types (Figure 9).

Histologically, characteristic changes can be found in the epidermis, dermis, and underlying vasculature.[75] The epidermis demonstrates focal parakeratosis, mild to moderate acanthosis, focal areas of spongiosis, minimal necrotic keratinocytes, minimal vacuolar degeneration of the basal layer, focal invasion of small numbers of lymphocytes with a T-cell predominance and erythrocytes. The dermis shows edema, mild superficial perivascular lymphohistiocytic infiltrate with mild obscuring of the dermoepidermal junction, and occasional extravasated erythrocytes. Additionally, dilation of superficial vessels is seen, with no invasion of vessels walls by inflammatory cells.[75]

Differential diagnosis

PLC can easily be confused with various other dermatoses, with lymphomatoid papulosis being the most common. Other disorders included pityriasis lichenoides et varioliformis acuta which presents with acute onset hemorrhagic and crust papules with a dense, wedge-shaped lymphohistiocytic infiltrate in the dermis, necrosis and dermal hemorrhage.[75] PLC also resembles arthropod bite reaction, varicella, other viral exanthemas, Gianotti-Crosti syndrome, erythema multiforme, pityriasis rosea, guttate psoriasis, vasculitis, and secondary syphilis.[75]

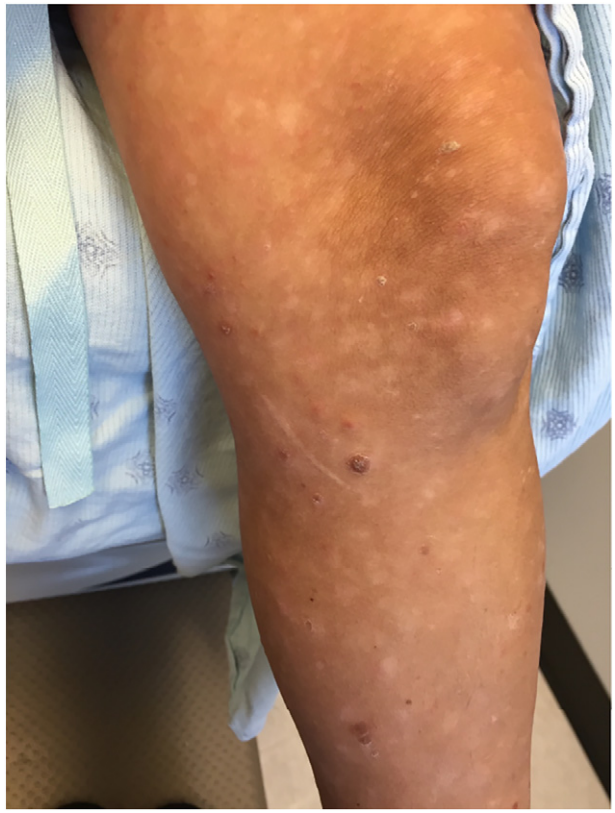

Fig. 9 Pityriasis lichenoides chronica.

Laboratory studies

Immunopathologic evaluation, cultures, and antibody tests may be implemented to exclude diseases listed in the differential diagnosis section.

Treatment

PLC is a benign, nonscarring condition which self-resolves over months to years. Treatment is aimed at balancing safety profile with effective care. First-line treatments include topical corticosteroids, oral antibiotics, and phototherapy. Second line treatments include ultraviolent B (UVB) or psoralen ultraviolent A (PUVA) light treatments. Methotrexate, acitretin, dapsone, or cyclosporine are reserved as third-line treatments.[75]

The efficacy of corticosteroids has not been proven over placebo or other treatments and concern for their side effect profile has led to trials of nonsteroidal topical immune-modulating therapies. Topical 0.03% and 0.1% tacrolimus ointment have been studied and shown to lead to complete clearance of PLC and refractory PL.[77,78]

Oral antibiotic agents used for treatment include tetracyclines and erythromycin. Dosages studied include 2 to 4 weeks course of 2 g of tetracyclines a day and 200 mg of erythromycin three to four times a day which have shown either complete or partial resolution.[75] Methotrexate has also been studied at a

dosage of 7.5 to 30 mg per week and patients with PLC were reported to have done well.

Prognosis

PLC has a benign course, though relapses are common and clinical manifestations may persist for months to years.[76] Transformation into malignant disorder is controversial, however, rare case reports have noted transformation to cutaneous T-cell lymphomas.

Tinea versicolor

Definition

Tinea versicolor (pityriasis versicolor) is a very common benign superficial skin infection usually manifesting as hypopigmented or hyperpigmented macules. In contrast to other infections designated with the term tinea, tinea versicolor is not dermatophytic; the causative agent is the saprophytic yeast *Malassezia globosa* and sometimes other *Malassezia* species.[79] Although it responds well to topical antifungal therapy, the rate of recurrence is very high.

Etiology and pathogenesis

The *Malassezia* species is a normal component of the dermal flora. The development of clinical disease occurs when the *Malassezia* fungus transforms from a cellular state to its mycelial form. As a lipid-dependent dimorphic fungus normally residing on healthy skin, extrinsic factors such as hyperhidrosis, application of oily creams, hot weather, and high ambient humidity are suspected to contribute to the conversion to a pathogenic mycelial yeast.

The development of macules occurs when the *Malassezia* yeast metabolizes fatty acids on the skin and release metabolites, including azelaic acid. Azelaic acid inhibits dopa-tyrosinase enzymes, effectively blocking the conversion of tyrosine into melanin, causing the hypopigmentation seen in this disease.[80] The pathology behind the development of hyperpigmented macules has been explained by a larger presence of *Malassezia* hyphae in the hyperpigmented lesions compared with those that are hypopigmented, causing a hyperemic inflammatory response in the pigmented lesions.[81] This superficial perivascular lymphocytic inflammatory cell infiltrate is thought to stimulate melanocytes to produce more pigment.[82]

Clinical and histologic manifestations

Lesions manifests as hypopigmented or hyperpigmented macules and sometimes with extremely thin plagues covered with fine desquamation (Figure 10). The most common presenting colors are white-tan, pink due to mild inflammation, and brown. Some patients complain of mild pruritus. With time, lesions often coalesce. The affected areas are usually found on the upper portion of the trunk and proximal areas of the arms, but also occur on the face, neck, and groin.

Biopsies are not usually necessary for diagnosis but if done, hypopigmented regions will show relatively normal skin with yeast and short hyphae. A biopsy of a hyperpigmented macule will reveal large melanosomes in a greater abundance than in nonlesional skin.

Differential diagnosis

Tinea versicolor may resemble vitiligo, which features completely depigmented lesions in contrast to the hypopigmented lesions of tinea versicolor. Hypopigmented lesions can also resemble pityriasis rosea, where a large herald patch will precede the widespread eruption of erythematous lesions with a collarette of scale. PA can be ruled out by distribution, as it presents on the face and less frequently on the arms. Secondary syphilis can also present with erythematous brown macules, but very often involves the palms and soles. The scale is central as opposed to the tinea versicolor scale that is peripheral.

Laboratory studies

A potassium hydroxide preparation is an easy way to confirm diagnosis of tinea versicolor. It will reveal both yeast and hyphal forms, closely resembling "ziti pasta and meatballs." Similarly, a Wood lamp examination will show fluorescence.

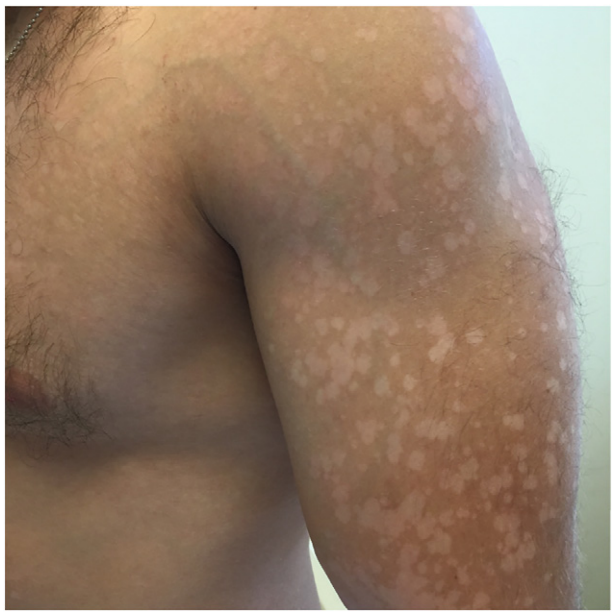

Fig. 10 Tinea versicolor.

Treatment

Initial therapy can be accomplished by a long course of topical therapy or a relatively shorter course of oral medication. Oral fluconazole 300 mg may be taken weekly for 1 to 4 weeks. If topical therapy is desired, antifungal shampoo (selenium sulfide 1% or 2.5%, ketoconazole 1% or 2%, zinc pyrithione, or ciclopirox olamine) in combination with an antifungal cream (topical azole antifungals or ciclopirox 1%) is applied once or twice daily for 2 months to several weeks. With more extensive involvement, oral therapy with fluconazole 200 mg daily for 5 to 7 days, or itraconazole 200 mg daily for 5 to 7 days can be considered.[83]

Prognosis

Tinea versicolor may recur almost annually for several years, possibly because the yeast represents the fungal transformation of normal skin flora.

Vitiligo

Definition

Vitiligo is an acquired chronic disorder characterized by completely white circumscribed macules from depigmentation resulting from the loss of melanocytes. With a worldwide occurrence of 0.5% to 2% of the population, vitiligo is a multifactorial autoimmune disease, but it is rarely associated with systemic autoimmune or endocrine disease.[84,85] The average age of onset is usually 20 years for patients to present with visually evident patchy depigmentation, but the age range may vary from toddlers to seniors.

Etiology and pathogenesis

Vitiligo is the most frequent cause of depigmentation, with no sex, racial, or socioeconomic predilections.[86,87] Several plausible pathogenic hypotheses have been proposed, increasingly suggesting that multiple mechanisms may contribute to the loss of melanocytes in vitiligo.

The presence of activated cytotoxic T-cell infiltrates in perilesional skin points to an autoimmune origin, and purified isolates of these T cells can induce melanocyte apoptosis in autologous nonlesional skin explants.[88,89] Additionally, the presence of antibodies to components of melanocytes are found in the sera of vitiligo patients, further supporting the autoimmune pathology of the disorder.[90,91]

Large-scale genome-wide association studies identified and confirmed at least 36 different genetic loci that contribute to vitiligo susceptibility.[92] Studies report 25% to 50% of vitiligo patients have affected relatives, with a 6% prevalence in siblings; however, concordance in monozygotic twins remains at 23%, suggesting that other factors play a significant role in vitiligo pathogenesis.[92–94]

Laboratory findings support a neural hypothesis, stemming from the observation that the distribution of depigmented patches can be related to dermatomes, despite being almost never strictly dermatomal.[95] The neural hypothesis posits that nerve endings secrete a neurochemical mediator that is cytotoxic to the melanocytes, which is supported by axon degeneration in dermal nerves of vitiliginous skin, but not in dermal nerves of nonlesional skin.[96]

Several studies also suggest that the initial event of melanocyte destruction may be due to oxidative stress.[86,97] Vitiligo patients have been reported to have low catalase and glutathione levels in peripheral blood and display depleted antioxidants in the epidermis.[98] Altered tetrahydrobiopterin homeostasis in lesional skin of patients with vitiligo are also thought to result in increased levels of reactive oxygen species and toxic metabolites.[99]

Clinical and histologic manifestations

Vitiligo presents with completely amelanotic macules and patches, which are typically milk- or chalk-white in color (Figure 11). The lesions have well-demarcated borders and may vary in size. Although the lesions enlarge centrifugally over time, they are typically asymptomatic and lack signs of inflammation. Although vitiligo lesions can develop anywhere on the body, it has a predilection for the face, acral areas, axillae, joints, and anogenital regions. Hairs in lesional skin can be depigmented, with the incidence of leukotrichia varying from 10% to greater than 60%.[100] Vitiligo of the scalp typically presents with poliosis (circumscribed areas of white hair).

The clinical classification of vitiligo falls into three general types:

1. Segmental vitiligo can present as multiple affected areas that almost completely respects the body midline. Segmental vitiligo also includes involvement of body hair, and is the subtype most strongly associated with leukotrichia.
2. Nonsegmental vitiligo is bilateral and often symmetrical.
3. The unclassified forms include findings in only the mucosa, or an isolated white macule.

Although a skin biopsy is not routinely required for diagnosis, the histology will reveal a complete loss of melanin pigment and an absence of melanocytes. Perilesional skin usually shows focal spongiosis and lymphocytes at the advancing border, and immunohistochemical staining will reveal a preponderance of CD8+ T cells in the inflammatory infiltrate at the dermoepidermal interface.[101,102]

Differential diagnosis

Lesions with only a partial loss of pigment may be distinguished from tinea versicolor, leprosy, or postinflammatory hypopigmentation. If the presenting hypopigmentation is a

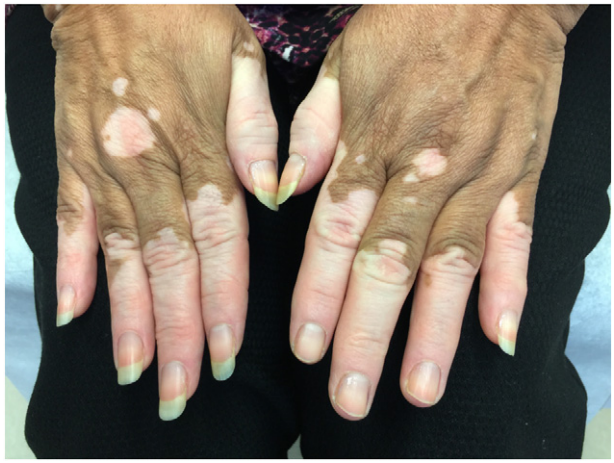

Fig. 11 Vitiligo.

single circular lesion, HN of Sutton should be considered and can be distinguished by its early onset. With complete depigmentation, chemically induced leukoderma should be considered. Overtreatment with potent topical corticosteroids, imatinib, and hydroquinone may lead to hypomelanosis that could resemble vitiligo.[103–105]

The diagnosis of vitiligo can be confirmed with a Wood lamp examination, where the depigmented lesion reveals a sharply demarcated area that emits a bright blue-white fluorescence.[87,106] Dermatoscopy can aid in differentiating vitiligo patches from other hypopigmentation disorders such as IGH and tinea versicolor, where vitiligo patches usually reveal normal texture skin and a residual perifollicular pigmentation absent in other hypopigmentation conditions.[107]

Treatment

Due to the effect of vitiligo on psychologic wellbeing and overall quality of life, the goals of vitiligo treatment are repigmentation and stabilization of depigmentation. Choice of therapy should depend on the extent of the disease as well as the patient's skin type and motivation to undergo treatment.

For small localized patches, treatment options include topical corticosteroids, topical calcineurin antagonists, and topical low-dose 8-methoxypsoralen (0.1%) with UVA.[108–110] The topical calcineurin antagonists may have increased efficacy if used under occlusion, and it has also been shown to have some success when used in combination with topical corticosteroids, narrow-band UVB, and PUVA. Patients with coexisting melasma have better repigmentation in response to narrow-band UVB compared with patients without melasma.

For widespread disease, systemic therapy with 8-methoxypsoralen, 5-methoxypsoralen, or 4,5,8-methyoxypsoralen along with UVA may be beneficial. PUVA therapy both increases the number of active melanocytes and reduces melanocyte degeneration; however, PUVA therapy may require 100 to 300 treatment sessions to achieve complete repigmentation.[111–113] Furthermore, burns resulting from PUVA phototherapy may be associated with extreme pruritus, even leading to prurigo nodularis in some cases.[114] For fewer phototoxic effects, narrow-band UVB radiation and 5-methoxypsoralen with UVA is an effective alternative.

In patients with refractory disease, the most effective surgical methods are thin split-thickness, punch, and suction blister epidermal grafting.[96,115,116] For affected eyelid and eyebrow, single hair grafting is effective.[115] For stable mucosal involvement, cosmetic tattooing is useful.

The most recently approved therapy for vitiligo is the use of 308-nm excimer laser with or without tacrolimus and pimecrolimus. A better repigmentation response is achieved when the laser therapy is initiated an earlier stage of the disease.

For patients with extensive disease who have failed repigmentation therapy and desire skin color matching, depigmentation can be performed with 20% monobenzyl ether of hydroquinone. Excellent but irreversible results are achieved with twice-daily use for 9 to 12 months.[83]

Spontaneous repigmentation infrequently may occur, but about one-third of patients experience partial repigmentation in sun-exposed patches. Most patients experience at least 75% repigmentation when adhering to first-line therapies, with about 25% improvement after 3 months of therapy, 50% improvement after 6 months, and 75% improvement after 9 months. A favorable repigmentation response is also achieved if the 308-nm excimer laser is used for a longer time and starting at an earlier stage of the disease. Current predictors of an inferior treatment response include poliosis, segmental distribution, and long-standing disease.

Prognosis

Although vitiligo does not cause physical impairment, the disease can cause significant psychologic and social distress which can lead to an impairment of the patient's quality of life. Additionally, the lack of melanin pigment in the lesions increases the patient's risk of sunburn and the subsequent risk of skin cancer in the amelanotic areas.

Waardenburg syndrome

Definition

Waardenburg syndrome (WS) is a genetically inherited disorder characterized by depigmentation, sensorineural hearing loss, and other developmental defects such as dystopia canthorum. Depigmentation occurs in the skin, hair, and iris. It exists in four subtypes. WS gene mutations exhibit high variable expressivity so patients do not have all clinical manifestations.[117]

Etiology and pathogenesis

WS is a rare syndrome with an estimated prevalence of 1 per 42,0000. It is responsible for 1% to 3% of total congenital deafness.[118] It was first described in fair-skinned populations in European cohorts, but it occurs in many ethnic groups throughout the world with the highest incidence reported among Kenyan Africans.[119]

The majority of patients with WS, WS types I, II, and III, exhibit autosomal dominant inheritance with a large variation in expression. Type IV is thought to follow an autosomal recessive pattern of inheritance.[119] WS is associated with six different genes: *PAX3* (paired box 3 transcription factor), *MITF* (microphthalmia-associated transcription factor), *EDN3* (endothelin 3), *EDNRB* (endothelin receptor type B), *SOX10* (Sry bOX10 transcription factor), and *SNAI2* (snail homolog 2), with different frequencies.[120] *PAX3* is associated with types I and III; *MITF* and *SNAI2* with type II; *EDNRB* and *EDN3* with type IV; and *SOX10* with types II and IV.[117] Mouse models have suggested that these genes are necessary for normal development of melanocytes.[121]

There exist several hypothesizes regarding the pathogenesis of the clinical features of WS. First, the "deficient neural crest" theory, suggests a developmental abnormality of the neural crest leads to the disease. This theory is supported by the association of WS with Hirschsprung disease. The next theory suggest WS is a part of the first pharyngeal arch syndrome. Another suggestion a relationship between WS and status dysraphicus, the failure of fusion of midline structures[117]; however, none of these theories explain all clinical features of WS.

Clinical and histologic characteristics

WS was first described in 1951 with six main features: (1) deaf-mutism, (2) white forelock, (3) heterochromia iridis, (4) dystopia canthorum, which is lateral displacement of the medial canthi combined with dystopia of the lacrimal punctum and blepharophimosis, (5) prominent broad nasal root, and (6) hypertrichosis of the medial part of the eyebrows.[117]

Type I WS can exhibit all of the symptomatology of the disease in addition to narrow nose with marked hypoplasia of nasal bone, short philtrum, and short, retropositioned maxilla. Type III has all the features of type I but additionally includes musculoskeletal abnormalities. Type II is characterized by deafness and heterochromia iridis. A subtype of type II is characterized by OA. Type IV is significant for its association with Hirschsprung disease in additional to WS craniofacial and pigmentary abnormalities.[117] All types may experience sensorineural hearing loss; however, hearing loss is not a universal feature, affecting between 36% and 58% of type I WS and up to 87% of type II.[119]

Pigmentary abnormalities in WS affect the skin, hair, and eyes (Figure 12). Cutaneous findings in WS are of two varieties: (1) achromic spots with sharp, irregular borders with surrounding hyperpigmented macules, reminiscent of piebaldism lesions and (2) scattered hyperpigmented macules which give skin a "patchy" appearance.[117] Hair findings include white forelock and premature graying of scalp, eyebrow, and body hair. Ocular pigmentation abnormalities include heterochromia iridis, bilateral isohypochromia iridis (pale blue eyes), and fundus pigmentary alterations such as albinotic fundi (generalized decrease in retinal pigment).[117]

Histopathologic examination of achromic skin in WS show absent melanocytes, indeterminate dendritic cells, or melanosomes in the keratinocytes.[117]

Differential diagnosis

The differential diagnosis of WS includes piebaldism, which has similar pigmentary disturbances of the skin and hair. OA must be distinguished from WS type II as both cause prominent ocular depigmentation. Neither OCA nor piebaldism have hearing or craniofacial involvement.

Treatment and prognosis

There is no effective treatment for WS. Early diagnosis of hearing defects in children and intervention with hearing aids or cochlear implants is important for psychologic development. Proper sun protection is necessary for both cutaneous and ocular findings to prevent complications. WS does not progress or affect life-expectancy giving it a favorable prognosis; however, given the physical manifestation of the syndrome it can be psychologically distressing to affected individuals and care should be given to attend to these concerns.

Additional white diseases

Hand-arm vibration syndrome (vibration white finger)

Hand-arm vibration syndrome (HAVS), formerly known as vibration white finger results from using jack

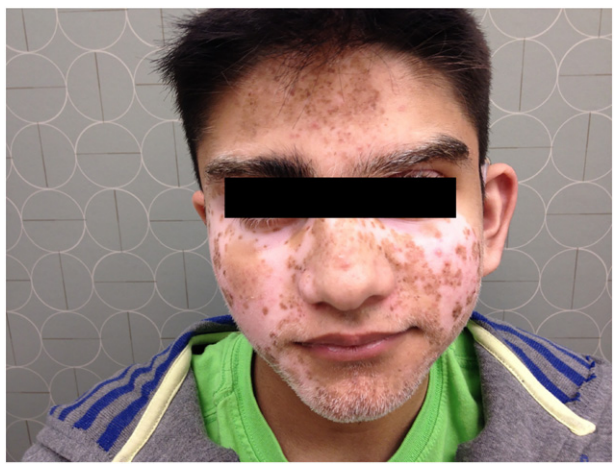

Fig. 12 Waardenburg syndrome.

hammers and other power tools. Since its first description in 1911, this syndrome has become one of the most common described diseases in the industrialized world.[122] Although the exact pathogenesis remains unclear, HAVS is believed to be a vascular process that is a secondary Raynaud phenomenon.

The classic findings for HAVS is finger blanching on exposure to cold or damp conditions. This is associated with numbness and reduced sensitivity secondary to the vascular nature of the disease. Blanching attacks last 1 to 60 minutes and are more common in the morning. Attacks become more frequent and prolonged with continued vibration exposure.[122] Biopsies of affected fingers show thickening of the media layer of arties with individual muscle cell hypertrophy; peripheral demyelination with increased Schwann cells and fibroblasts; and increased connective tissue causing perivascular and perineural fibrosis.[122] The mainstay of treatment is abstinence from the vibration exposure. Warming the hands is also thought to provide relief.

Lead-based cosmetics

Mention should be made of lead-based make-up in previous times, when it was in vogue to have a perfectly white face. White lead is basic lead carbonate formed by placing lead sheets in acetic acid and heating it to form a white powder.[123] Donning white lead paint on the face first became in fashion during the reign of Queen Elizabeth I of England in the 16th century.[124] Not until the mid-18th century that the use of lead carbonate was recognized as dangerous, when the death of the Countess of Coventry was attributed to her cosmetics. The use of such cosmetics into the 19th century, culminating in the use of Laird's Bloom of Youth and the catastrophic results.[124] This lotion contained a mixture of lead acetate and carbonate whitening cream, resulting palsy, fatigue, emaciation, and paralysis of the neck and extremities.[123] One such case had paralysis so severe she could not hold her head erect without a supporting apparatus.[124]

Lead poisoning results from repeated exposure to lead-containing compounds and subsequent accumulation in tissue. Signs and clinical manifestations may develop gradually or occur suddenly. All systems of the body are affected, especially the neuromuscular system, the gastrointestinal tract, and the hematopoietic tissue. Victims typically become pale and irritable and complain of insomnia and a metallic taste in their mouth.[123]

Postinflammatory hypopigmentation

Postinflammatory hypopigmentation can occur following cutaneous inflammation, injury or dermatological treatment such as dermabrasion and chemical peels.[125] Such hypopigmentation, sometimes referred to as guttate hypomelanosis, can occur in patients with darker skin and may be due to exposure to chemicals splattering during household chores (such as mopping a floor with bleach), sitting in front of Franklin stove with sparks flying from the burning wood or hot coals, or even standing in front of a stove while frying, or the spray of hot fat. Additionally, tattoo removal, especially when done with lactic acid, may be associated with hypertrophic scars and hypopigmentation following their use.[126]

The pathogenesis of postinflammatory hypopigmentation related to injury to melanocytes which are known to react with normal, increased, or decreased melanin production in response to inflammation or trauma.[125] The shape, size, and distribution of the lesions rely on the mechanism of injury and color ranges from hypopigmentation to depigmentation. Management begins with the removal of the offending agent. Pharmacologic treatment may be offered with twice-daily application of a medium-potency topical steroid in combination with a tar-based preparation. Twice-daily application of 1% pimecrolimus cream for 16-weeks has been successfully utilized as well.[125]

Skin bleaching

In other cases, there has been bleaching of the skin, as in the case of Michael Jackson, with various peels, or the use of such concentrations of hydroquinone much higher than the 4% allowed in the United States. Skin lightening agents including hydroquinone, topical steroids, and mercury are widely used for treatment of melasma and postinflammatory hyperpigmentation[127]; however, use of these agents may be associated with a wide range of adverse systemic effects, including nephropathies, neurologic changes, and increased risk for SCC, when abused. The use of these skin compounds is commonplace in Africa, with an estimated prevalence of 25% to 96%, leading to a high incidence of toxicity in this population.[127,128]

Ultraviolet light–induced leukoderma

Mottled leukoderma of the scalp of patients with dark skin and androgenic alopecia is associated with UV-light exposure. This leukoderma may initially be confused with vitiligo. The pathogenesis of these lesions is a result imbalance of antioxidants and pro-oxidants secondary to lack of usual protection of scalp by hair follicles.[129]

X-linked dominant chondrodysplasia punctata (Happle syndrome)

X-linked dominant chondrodysplasia punctata or Happle syndrome is rare disorder characterized by growth retardation, cataract, and temporary ichthyosiform erythroderma. Additionally, cutaneous findings may be found including atrophic lesions, hyperkeratotic papules, and disturbances of hair growth follow the lines of Blaschko. Furthermore, it has been shown that depigmentation of the eyelashes may be associated with this disorder.[130]

Conclusions

White diseases are an extremely common dermatologic phenomenon. Many depigmentation pathologies are permanent. Without the sun-protective effects of melanin, these individuals are more susceptible to skin cancers than the general population. In addition to medical and cosmetic treatment for white diseases, sun-protective measures are a necessity for this patient population. Despite this, diseases of hypopigmentation are relatively benign, especially in comparison with their inverse condition, diseases of hyperpigmentation. The only white diseases associated with mortality are systemic Degos disease and Chediak-Higashi syndrome, a variant of albinism associated with immunosuppression. Conversely, diseases of hyperpigmentation, such as melanoma, carry a more ominous prognosis.

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