Acquired disorders with depigmentation: A systematic approach to vitiliginoid conditions

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Learning objectives

After completing this learning activity, participants should be able to identify treatment regimes for hypopigmented dermatoses; list methods to manage hypopigmented dermatoses; and recognize and classify complications related to the hypopigmented dermatoses.

Disclosures

Editors

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Acquired disorders with depigmentation are commonly encountered by dermatologists and present with a wide differential diagnosis. Vitiligo, the most common disorder of acquired depigmentation, is characterized by well-defined depigmented macules and patches. Other conditions, such as chemical leukoderma, can present with similar findings, and are often easily mistaken for vitiligo. Key clinical features can help differentiate between acquired disorders of depigmentation. The first article in this continuing medical education series focuses on conditions with a vitiligo-like phenotype. Early recognition and adequate treatment of these conditions is critical in providing appropriate prognostication and treatment. (J Am Acad Dermatol 2019;80:1215-1231.)

Key words: Alezzandrini syndrome; chemical leukoderma; extramammary Paget disease; halo nevi; lichen sclerosus; melanoma-associated leukoderma; onchocerciasis; pinta; scleroderma leukoderma; Vogt-Koyanagi-Harada.

Acquired disorders with depigmentation are associated with social stigmatization and a reduced quality of life.[1-4] Vitiligo is the most common of these disorders and can present with well-defined depigmented macules and patches that can be localized or generalized. However, a

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Table I. Comparison of nonsegmental vitiligo, segmental vitiligo, and focal vitiligo

	NSV	SV	FV*[12-14]
Typical onset	Childhood and adulthood	Childhood	Adulthood
Distribution	Symmetrical tendency at sites susceptible to friction, including the extensor sites and orifices	Asymmetrical and does not cross midline; uni- or multisegmental; most common site is the face followed by the trunk	Head and neck (63%), genitals (23%), hands (5%), and trunk (3%); can be found in conjunction with genital melanosis in rare cases[15]
Leukotrichia	Absent early	Present early	Present
Koebnerization	Frequent (30%)	Rare	Rare
Progression	Unpredictable†: tendency to slowly progress in an unpredictable pattern with or without periods of rapid progression	Predictable: rapid progression over 3-24 months over a dermatome, then ceases	NSV progression‡: 23-27% within 2 years; SV progression: 0-7% within 1 year; remains focal: 77%
Key differentials	Chemical leukoderma, MAL, HMF, and VKHD	Segmental nevus depigmentosus	Lichen sclerosus, spontaneous neoplastic regression, chemical leukoderma, trauma-induced depigmentation, and DEMPD

DEMPD, Depigmented extramammary Paget disease; *FV*, focal vitiligo; *HMF*, hypopigmented mycosis fungoides; *MAL*, melanoma-associated leukoderma; *NSV*, nonsegmental vitiligo; *SV*, segmental vitiligo; *VKHD*, Vogt-Koyanagi-Harada disease.

*Focal vitiligo is characterized by depigmentation involving a small area of skin that does not evolve into NSV or SV after 1 to 2 years.[12-14]

†To a lesser extent, some predictions can be made. Approximately 74% of patients with NSV have progressive disease. The risk of progression is >90% when the posterior trunk, hands, or feet are the initial site of involvement. Progression is usually contingent to the initial site; however, when the hand is the initial site, progression to the face is most frequent, giving rise to the classical acrofacial distribution.[16]

‡The frequencies provided for progression of focal vitiligo are based on 2 case series.[13,14]

vitiliginoid (vitiligo-like) phenotype can be present with many other conditions. Identifying vitiliginoid conditions early in the disease process can reduce unnecessary interventions and prevent disabling complications. The purpose of this article is to review acquired vitiliginoid disorders and to describe features that help distinguish them from vitiligo. A summary of the features of vitiligo is provided in Table I.[5-16]

VITILIGINOID DISORDERS

Vitiliginoid disorders are classified as either generalized or localized based on the extent and distribution of depigmentation. In this review, we define depigmentation as the complete absence of pigment in the skin, while hypopigmentation is reduction of epidermal pigment. The clinical distinction between the two can be difficult. A Wood's lamp or a handheld black light source accentuates depigmented skin and can be used to differentiate between hypopigmented and depigmented lesions (Fig 1).[17-22] In the absence of epidermal melanin, a potent absorber of ultraviolet light, underlying fluorescent compounds of the skin give a characteristic chalky bluish-white appearance.[23] The second article in this continuing medical education series addresses acquired disorders that present primarily with hypopigmentation.

GENERALIZED DEPIGMENTATION

The disorders described in this section can initially be localized; however, the distribution of depigmentation often progresses to involve multiple body surfaces. The most important aspect of evaluating patients with depigmentation is a thorough history and physical examination. Chemical leukoderma, melanoma-associated leukoderma, Vogt-Koyanagi-Harada disease, and scleroderma leukoderma can all have cutaneous and histologic features that are identical to vitiligo.[24-27] The diagnosis of these conditions can be established clinically, and histological confirmation is often unnecessary.[12] Obtaining a biopsy specimen should be considered in patients with depigmentation associated with epidermal changes (eg, atrophy), induration, sensory changes, alopecia, or depigmentation that is refractory to conventional treatment. An algorithm to classifying disorders with generalized depigmentation is presented in Fig 2.

Chemical leukoderma

Key points

- **All cases of chemical leukoderma are preceded by a history of repeated chemical insult**
- **Identifying and avoiding the offending agent frequently results in gradual repigmentation**

Fig 1. Comparison of depigmented and hypopigmented lesions under Wood's light examination. (**A**) Depigmented lesions autofluoresce bright white under a Wood's lamp; in contrast, (**B**) hypopigmented lesions under a Wood's lamp show an off-white accentuation without fluorescence. False positives results can be caused by numerous chemicals, including ink (especially highlighters), soap residue, lemon juice, sunscreen, or medications (eg, lint or tetracyclines).[17,18] (**A**, Reprinted from Larsabal et al[19] with permission from Elsevier. **B**, Reprinted from Hewedy et al[20] with permission from Elsevier.)

Chemical leukoderma is an acquired disorder that results from repeated exposure to certain chemicals in genetically susceptible individuals.[28,29] Phenol derivatives, catechol derivatives, and sulfhydryls are frequent culprits that put factory workers, cosmetologists, and pesticide handlers at risk (Table II).[30-33] Patch testing may be helpful in identifying the triggering agent responsible for chemical leukoderma, but requires high test concentrations and interpretation at 1 and 6 months.[30] A comprehensive list of chemicals associated with leukoderma is available.[30]

Chemical leukoderma is a clinical diagnosis that can be established by a history of repeated exposure to a known or suspected depigmenting agent plus acquired vitiligo-like depigmentation at the primary exposure site. Early in the disease, 90% of patients develop multiple confetti macules at the site of exposure that tend to become confluent over time (Fig 3).[24,30,35,36] A quarter or more of patients have depigmented findings at sites distant to the primary site, which often leads to a misdiagnosis of vitiligo.[30] A confetti pattern of depigmentation, which is associated with a higher frequency of the Koebner phenomenon (KP), can also be seen with vitiligo and may be a marker of rapid progression.[37] The absence of the KP and progressive depigmentation, rather than a cyclic and unpredictable progression, are more suggestive of chemical leukoderma. In cases of chemical leukoderma, there is a history of repeated chemical insult that precedes the cutaneous manifestations by 1 month to 24 years. Depigmentation that results after a single exposure to a chemical should be considered a result of a chemically induced koebnerization phenomenon associated with vitiligo or postinflammatory depigmentation.[30]

The management of patients with chemical leukoderma requires that the inciting chemical be

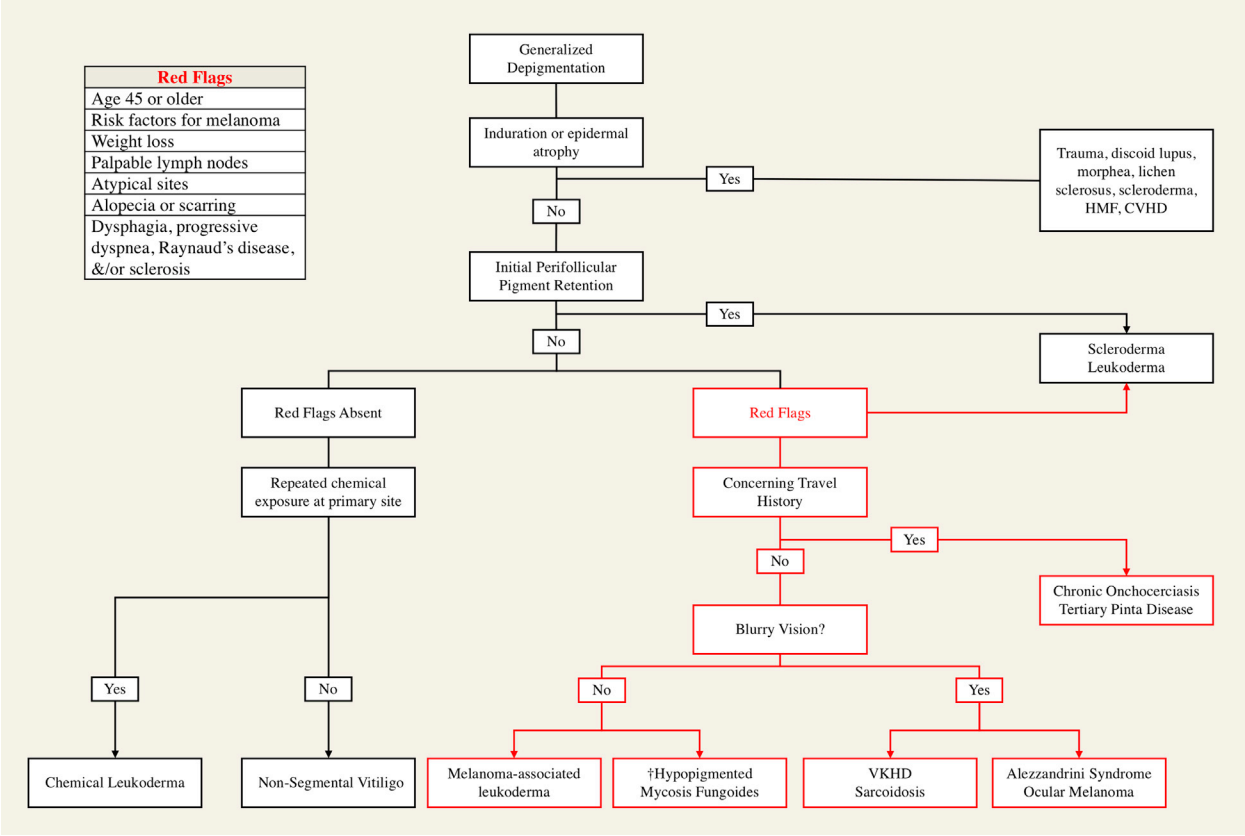

Fig 2. Proposed algorithm for approaching and classifying acquired disorders with generalized depigmentation. †Hypopigmented mycosis fungoides (HMF) can manifest with hypopigmentation, depigmentation, or both, and is discussed in the second article in this continuing medical education series. The presence of follicular papules, epidermal atrophy, or mottled pigmentation may be present and can help differentiate HMF from vitiligo; however, they are not sensitive findings. Obtaining multiple biopsy specimens is often required to establish the current diagnosis. *CVHD*, Chronic graft versus host disease; *VKHD*, Vogt-Koyanagi-Harada disease.

avoided. Subsequently, spontaneous, perifollicular repigmentation can gradually occur over a period of weeks to months. Occasionally, depigmentation progresses despite avoiding the chemical agent, a process often referred to as "chemical vitiligo." Treatment options are identical to vitiligo. In addition, to prevent recurrence or progression of skin depigmentation, patients should avoid exposure to all known depigmenting agents.[30]

Melanoma-associated leukoderma

Key points

- **Melanoma-associated leukoderma is not uncommon in patients with melanoma, particularly those treated with immune checkpoint blockade**
- **Skin depigmentation resembling vitiligo in patients >50 years of age warrants a thorough skin examination, including the mucosal membranes, in addition to a focused ocular examination**
- **The development of melanoma-associated leukoderma during immunotherapy is a marker of favorable prognosis**

Melanoma-associated leukoderma (MAL) is a T cell–mediated autoimmune disorder that occurs in 2% to 16% of patients with melanoma.[38,39] The pathogenesis of MAL remains unclear but appears to be different from vitiligo.[19,38,40] MAL can occur with primary or recurrent melanoma, metastatic melanoma, or during immunotherapy with programmed cell death 1 or cytotoxic T-lymphocyte antigen 4 inhibitors. Interestingly, the development of MAL during immunotherapy is a positive prognostic marker.[41-45]

The age of onset and presence of risk factors for developing melanoma help differentiate MAL from vitiligo. The median age of onset with MAL is

Table II. Common chemicals that may induce chemical leukoderma[30,32,33]

Chemical	Object
PPD	Hair dye, black socks, and shoes
MBH	Rubber (sandals, condoms, and gloves)
PTBP	Adhesive bindi,* perfume, deodorant, and insecticides
Azo dyes	Cosmetics

MBH, Monobenzyl ether of hydroquinone; *PPD*, paraphenylene diamine; *PTBP*, paratertiary butyl phenol.
*Commonly present in Indian culture is depigmentation caused by the sticky material used in bindi (red dot seen on the forehead of married women).[34]

55 years; in contrast, vitiligo rarely develops in patients >50 years of age.[39] Additional features that may be suggestive of MAL include the absence of KP, no family history of vitiligo, depigmentation localized to photoexposed areas, and multiple flecked depigmented macules (Fig 4).[19,40] Serum antibodies against melanoma antigen recognized by T cells 1 (MART1) may be a useful marker to help differentiate MAL from vitiligo.[38] Treatment of MAL is similar to vitiligo; however, systemic therapies should be initiated in consultation with the patient's oncologist.

Vogt-Koyanagi-Harada disease and Alezzandrini syndrome

Key points

- **Vogt-Koyanagi-Harada disease should be considered in adults with progressive depigmentation that coincides with visual disturbances**
- **HLA-DRB1*04 carriers are the primary group at risk for developing Vogt-Koyanagi-Harada disease**
- **If a delay in ophthalmologic evaluation is anticipated and the patient has acute visual symptoms, high-dose systemic corticosteroids should be initiated to prevent further vision impairment**

Vogt-Koyanagi-Harada disease (VKHD) is a sight-threatening condition that is characterized by systemic and cutaneous manifestations of T cell–mediated autoimmune dysregulation.[46-49] The disease targets melanocyte-containing tissues in the uvea, skin, inner ears, and leptomeninges, predominately in genetically susceptible carriers of HLA-DRB1*04 haplotypes.[50] The incidence is highest in females 20 to 50 years of age and in Asians, Indians, American Indians, Middle Easterners, and Mexicans.[51,52] A history of aseptic meningitis, uveitis, tinnitus, or hearing loss in a patient with

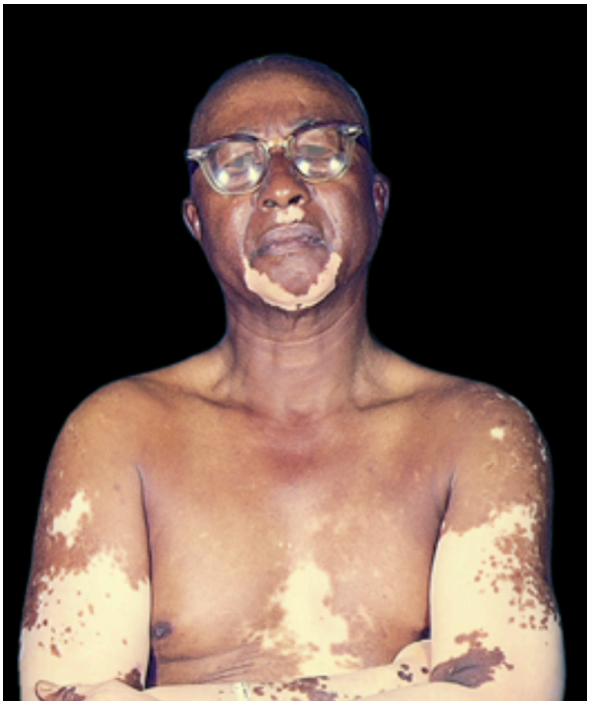

Fig 3. Chemical leukoderma in an African American factory worker depigmented from repeated exposure to monobenzyl ether of hydroquinone. (Reprinted from Goldsmith et al[36] with permission from McGraw-Hill Education. Copyright McGraw-Hill Education.)

depigmented patches suggest a diagnosis of VKHD.[52-54] Iris transillumination can be easily seen with severe depigmentation of the iris (Fig 5).[55] VKHD can be divided into 4 stages that are phenotypically distinct (Table III).[56-58] Alezzandrini syndrome, a condition related to VKHD, presents similarly but with unilateral symptoms.[59,60]

Any patient with progressive depigmentation and visual complaints should be referred to a retinal specialist; a delay in diagnosis and treatment is associated with a poor visual prognosis. If a delay in ophthalmologic evaluation is anticipated and the patient has symptoms suggestive of acute uveitis, high-dose systemic corticosteroids should be administered urgently to prevent sight-threatening complications.[46] The skin manifestations of VKHD are managed similarly to vitiligo.

Scleroderma leukoderma

Key points

- **Depigmentation associated with perifollicular pigment retention is characteristic of scleroderma leukoderma and resembles repigmented vitiligo**
- **Early juvenile localized scleroderma can present with cutaneous depigmentation that**

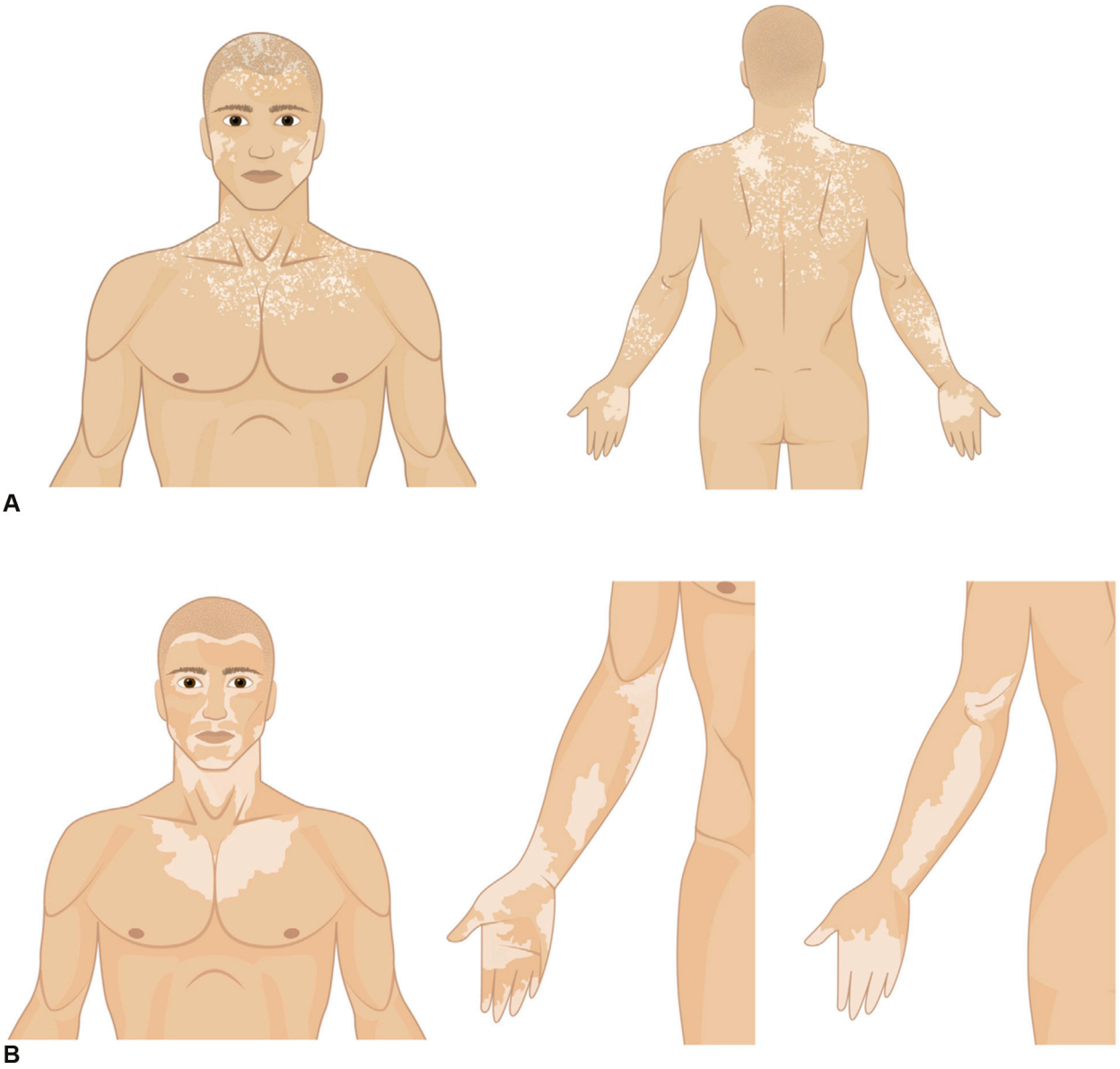

Fig 4. Pattern of depigmentation occurring in patients receiving anti–programmed cell death 1 (PD-1) therapy (**A**) and in those with vitiligo (**B**). **A**, Melanoma-associated leukoderma induced by PD-1 inhibitors are characterized by multiple flecked white macules localized on photo-exposed areas. **B**, Vitiligo is characterized by white patches symmetrically distributed and localized on the face (forehead and around the eyes, nose, ears, and mouth), hands (fingers and wrists), elbows, and trunk. (Reprinted from Larsabal et al[19] with permission from Elsevier.)

clinically and histologically resembles vitiligo

- **The management of scleroderma is complex and requires a multidisciplinary approach**

Systemic sclerosis (SS) is a multisystem immune-mediated disorder that is frequently associated with prominent pigmentary changes.[61] Three pigmentary variations have been described: vitiligo-like depigmentation (without fibrosis), diffuse hyperpigmentation accentuated in sun-exposed regions, and hypopigmentation/hyperpigmentation in areas of sclerosis.[62-64] The vitiligo-like phenotype or "salt-and-pepper" appearance is an early feature of SS that is characterized by depigmentation with perifollicular retention and that typically involves the retroauricular region, scalp, forehead, chest, or trunk (Fig 6).[62,65-68] A subset of children with early juvenile localized scleroderma (JLS) or hypopigmented morphea have lesions that clinically and histologically resemble vitiligo, often delaying the

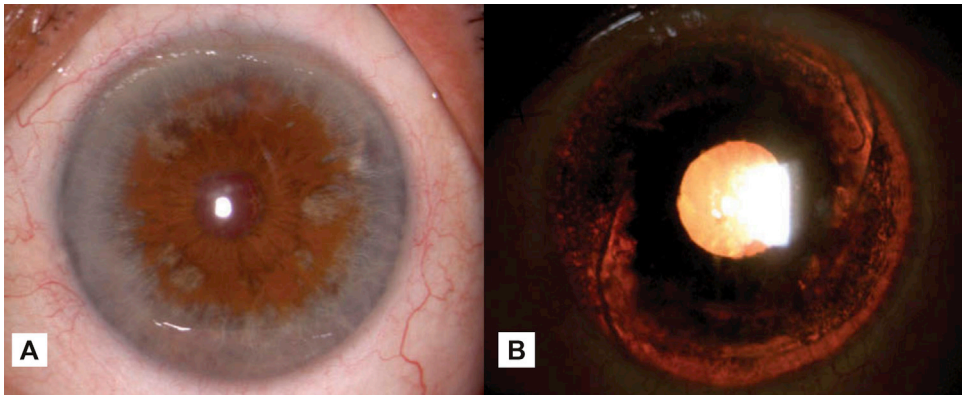

Fig 5. Bilateral iris depigmentation. Depigmentation of the (**A**) iris at the periphery results in (**B**) iris transillumination. (Reprinted from Cuevas et al[55] by permission of the publisher [Taylor & Francis Ltd, http://www.tandfonline.com]).

diagnosis of JLS by >2 years.[69] A reciprocal distribution of $CD34^+$ and $FXIIIa^+$ cells (ie, a significant reduction or absence of $FXIIIa^+$ and $CD34^+$ cells in the papillary dermis and reticular dermis, respectively, and an increase in $FXIIIa^+$ cells in areas of fibrosis) can help differentiate early JLS from vitiligo. Early diagnosis and adequate treatment may prevent disfiguring progression.[69]

Tropical diseases

Key points

- **Chronic onchocerciasis and tertiary pinta disease should be considered in migrants that have spent time in endemic regions**
- **Subcutaneous nodules, hypo- or depigmented skin changes, persistent eosinophilia, and a travel history to an endemic region is pathognomonic of chronic onchocerciasis**
- **Before treatment, patients with chronic onchocerciasis should be screened for *Loa loa* coinfection to prevent life-threatening encephalitis**

Chronic onchocerciasis and pinta disease are commonly neglected tropical diseases that are underdiagnosed or underreported in nonendemic areas.[70] These conditions can be imported to nonendemic regions and should be considered in tourists, immigrants, adoptees, and soldiers who have spent time in endemic regions. Because travel to tropical parts of the world has been increasing, it is imperative that the practicing dermatologist is able to recognize features of these disorders, conduct an appropriate work-up, initiate treatment, and manage complications.

Chronic onchocerciasis or "river blindness." Chronic onchocerciasis is an infectious oculocutaneous disease that is transmitted to humans by infected blackflies (*Simulium* spp).[71] Onchocerciasis is endemic in Brazil, Venezuela, Yemen, and 31 countries of sub-Saharan Africa.[70] The cutaneous manifestations are highly variable and related to the host's immunogenetics; the depigmentation phenotype is associated with DQA1*0501 and DQB1*0301 haplotypes.[72] Onchocercal depigmentation is characterized by nonpruritic depigmented patches with perifollicular pigment retention, classically distributed symmetrically over the anterior tibia, lateral groin, or lower abdomen (Fig 7, *A*).[70,73-75] Intermittent diffuse pruritus, persistent eosinophilia, subcutaneous nodules over bony prominences, and painless lymphadenopathy are other common features of onchocerciasis.[76] Skin biopsy specimens obtained from subcutaneous nodules often reveal mature onchocercas[70] (Fig 7, *B*) and "skin snips" from the anterior tibia and iliac crests can reveal migrating microfilaria[75] (Fig 7, *C*). Ocular complications are associated with high rates of morbidity but are preventable with appropriate treatment.

Before therapy, patients should be screened for *L loa* coinfection to prevent life-threatening encephalitis that can occur with a subclinical *L loa* coinfection.[77-79] Onchocerciasis is treated with a single dose of ivermectin (150 μg/kg) followed by a 4- to 6-week course of doxycycline (200 mg/day).[80,81] Within 24 hours of treatment, 10% of patients develop severe pruritus, tender localized lymphadenopathy, or edema. This reaction responds well to oral prednisone (40 mg/day) tapered over 5 days.[76,82]

Tertiary pinta disease. Pinta is caused by *Treponema carateum*, an endemic treponematosis that is transmitted by direct skin-to-skin contact.[83] The prevalence of pinta disease is unknown, but reported endemic regions include Mexico, Brazil, Colombia, the Caribbean islands, Cuba, and Peru.[84,85] Pinta disease naturally progresses through 3 stages and is the only spirochetal disease to have

Table III. Vogt-Koyanagi-Harada disease clinical stage

Stage	Findings
1: Prodromal	*Features:* aseptic meningitis (headache, periorbital pain, meningismus, nausea ± fever, dysacusis, or tinnitus); some subjects also complain of hyperesthesia of the hair and skin to touch *Duration:* complete resolution within 1-2 weeks
2: Acute (ophthalmic)	*Timing:* occurs within a few days (3-5 days) to weeks after the prodromal stage *Features:* bilateral acute blurring of vision,* sensorineural hearing loss, tinnitus, or vertigo; sudden decrease in vision is the most common compliant *Duration:* symptoms may last weeks to months; stage 2 may recur, resulting in episodic uveitis
3: Convalescence (cutaneous)	*Timing:* 3-12 weeks following acute phase, as symptoms improve *Features:* tissue depigmentation† (skin, hair, or eyes) or alopecia (noncicatricial) *Duration:* lasts months to years
4: Chronic or recurrent uveitis	*Timing:* variable *Features:* panuveitis with recurrent anterior uveitis episodes, which can result in retinal pigment epithelial disruption, cataracts, and ocular hypertension *Duration:* variable

The diagnostic criteria for Vogt-Koyanagi-Harada disease are included in Supplemental Table I. The American Uveitis Society has proposed a revised, widely accepted, diagnostic criteria for Vogt-Koyanagi-Harada disease.[56]
*Bilateral acute blurring of vision, 30% have a delay before the second eye is involved. Anterior uveitis follows posterior uveitis.[57]
†Depigmentation typically distributed over the scalp, face, and trunk, especially common over the sacrum.[57] Depigmentation of the corneal limbus may be the earliest finding (the Sugiura sign).[58]

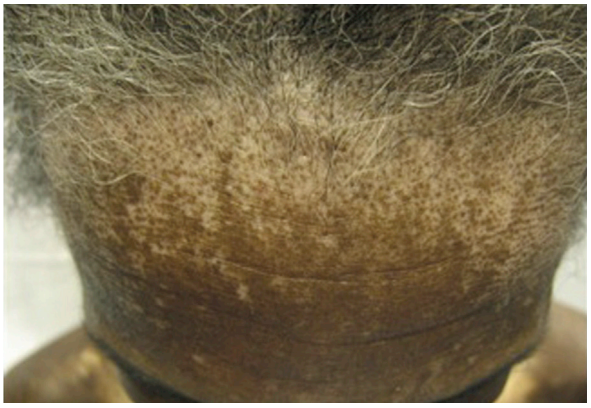

Fig 6. Scleroderma-associated depigmentation with preserved perifollicular pigmentation. The salt-and-pepper appearance resembles repigmented vitiligo. (Reprinted from Wigley and Boin[68] with permission from Elsevier.)

only cutaneous manifestations (Supplemental Table I; available at http://www.jaad.org). The late stage of pinta disease can manifest with symmetrical, treponema-free, depigmented patches that commonly involves the palms, wrists, elbows, and ankles[86,87] (Fig 8). Serology cannot differentiate between different treponema species. A single intramuscular dose of penicillin G benzathine (600,000 units for patients ≤10 years of age and 1.2 million units for patients >10 years of age) is recommended for all cases and close contacts.[88]

LOCALIZED DEPIGMENTATION

The conditions in this section, in contrast to the previously described disorders, remain localized to 1 area and do not progress to involve the skin in other body regions. Some disorders rarely manifest with acquired depigmentation involving only the hair.[89-98] An algorithm to classifying disorders with localized depigmentation is presented in Fig 9.[89-92,99]

Postinflammatory depigmentation

Key points

- **The primary morphology of the underlying inflammatory disease often provides a straightforward diagnosis**
- **Localized skin depigmentation can occur after corticosteroid injections or skin trauma that occurs after severe scratching, cryotherapy, burns, or laser**
- **Identifying and controlling or preventing the underlying etiology is the first step in managing postinflammatory depigmentation**

Postinflammatory depigmentation can occur as a result of injury or inflammation in the skin. The diagnosis is often straightforward when performing a thorough history and physical examination. Depigmentation can occasionally be the presenting feature of discoid lupus. Undiagnosed or untreated, discoid lupus can progress to form plaques with irregular hyperpigmented borders and central depigmentation.[100] These lesions are occasionally confused with inflammatory or marginal vitiligo.[100-103] Periorbital discoid lupus can present with depigmentation isolated to the lid margins without preceding erythema or plaque formation.[103] Severe scratching, corticosteroid injections[104-106]

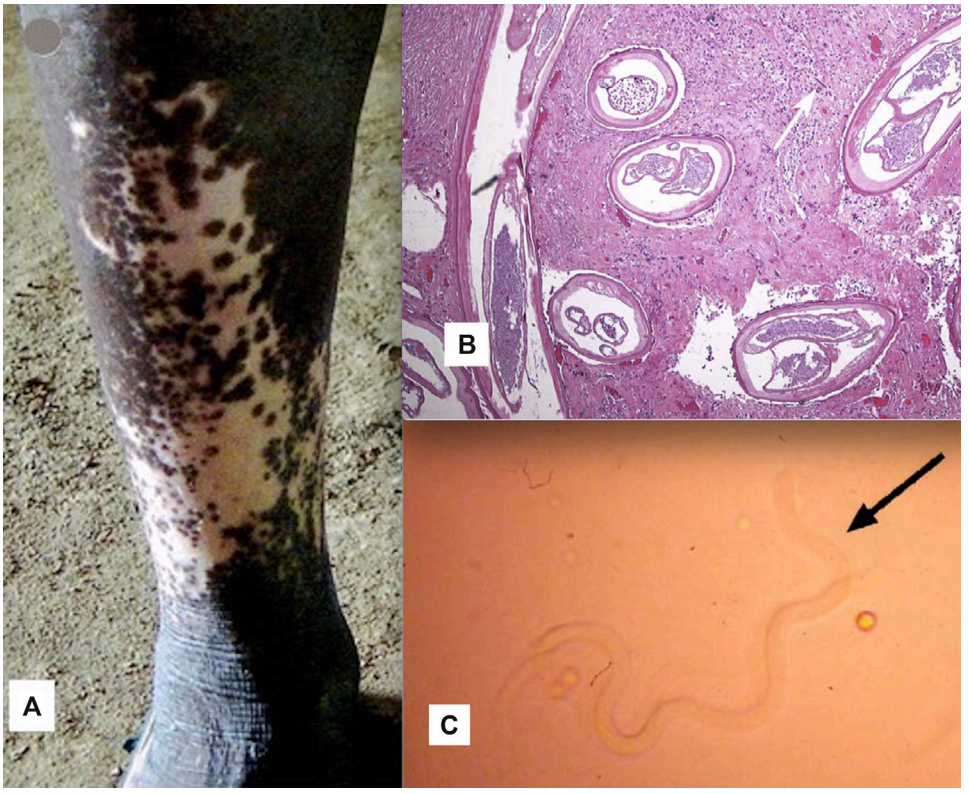

Fig 7. **A**, Chronic onchocerciasis. **B**, Adult worms. Hematoxylin–eosin stain of a nodulectomy specimen showing multiple adult worms. The white arrow indicates a microfilaria. **C**, Migrating microfilariae. Spirocete-like microfilaria emerging from the skin snip and observed microscopically. (**B** and **C**, Original magnification × 10. **A**, Reprinted from *The Lancet*, Taylor et al,[74] copyright 2010, with permission from Elsevier; **B**, reprinted from Antinori et al[70] with permission from Elsevier; and **C**, reprinted from Enk[75] with permission from Elsevier.)

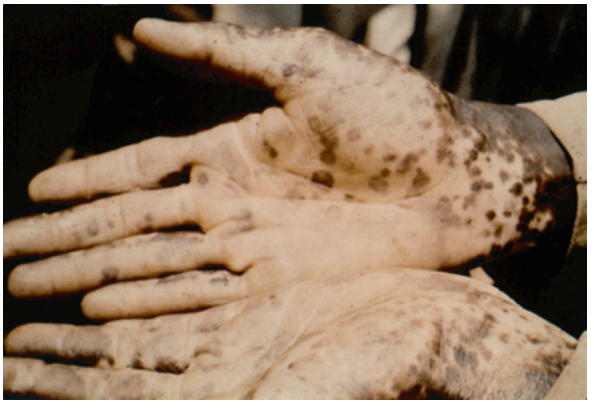

Fig 8. Tertiary pinta disease. Bilateral depigmented patches in tertiary pinta. (Reprinted from Goldsmith et al[87] with permission from McGraw-Hill Education. Copyright McGraw-Hill Education.)

(Fig 10), chronic graft versus host disease, cryotherapy, burns, and laser interventions are other potential causes of postinflammatory depigmentation. Depigmentation can be widespread when the underlying etiology is severe or uncontrolled. Identifying the underlying etiology is necessary to guide therapy and to prevent progression.

Spontaneous neoplastic regression

Key points

- **In children, halo nevi follow a benign course, and reassurance is appropriate when features of melanoma are absent**
- **A depigmented macule or patch can result from a completely regressed pigmented lesion**
- **Metastatic melanoma has no detectable primary site in 4% to 10% of cases; however, a depigmented lesion located on skin that drains to an enlarged lymph node is sometimes identifiable**

Depigmentation associated with spontaneous regression of neoplasms has been described with nearly all types of benign and malignant lesions.[107,108] Depigmentation of melanocytic lesions is often preceded by a halo, although depigmentation without a visible halo has increasingly been

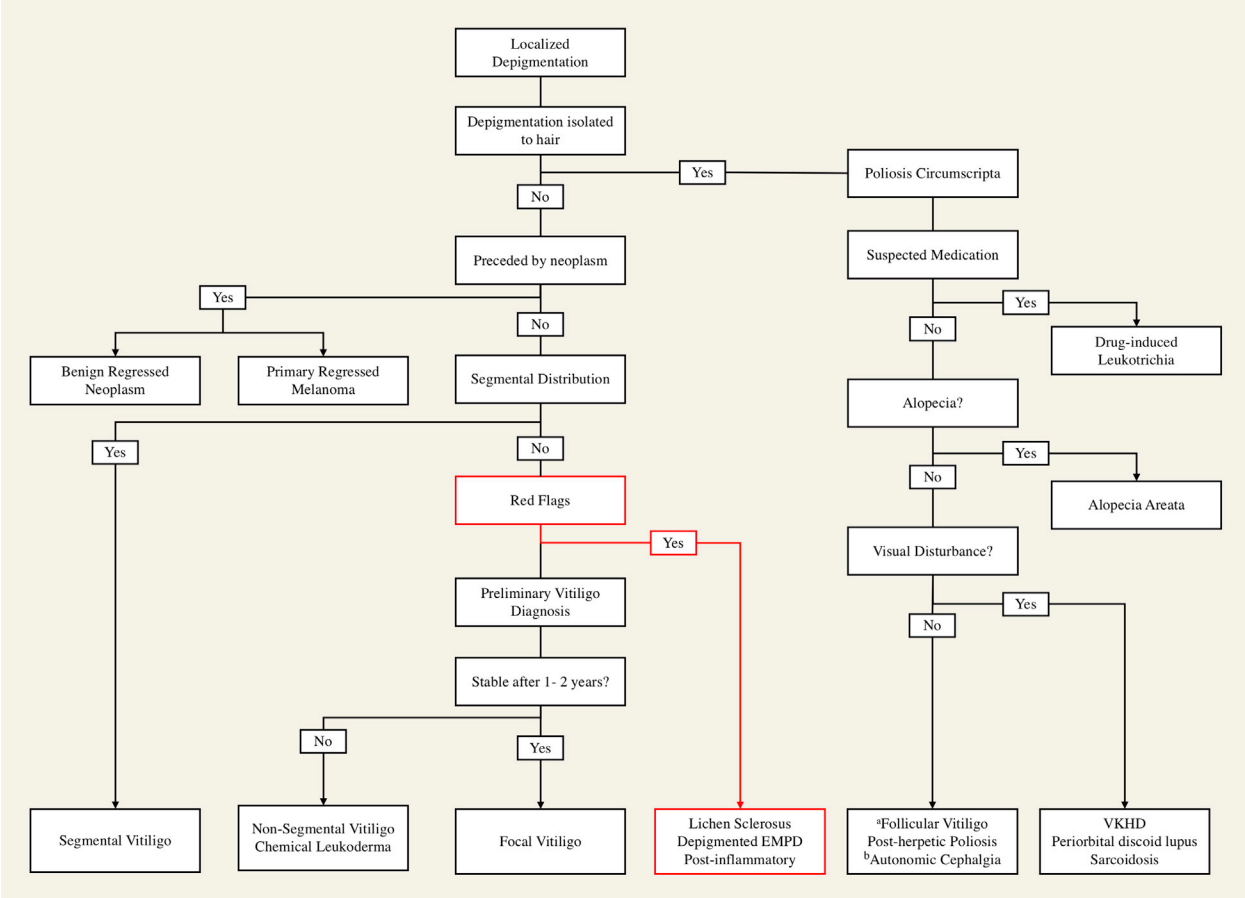

Fig 9. Proposed algorithm for approaching and classifying acquired disorders with localized depigmentation. [a]Follicular vitiligo is characterized by the rapid development of leukotrichia that precedes skin depigmentation and has a predilection for older males.[89-92] Migratory leukotrichia might also occur with follicular vitiligo.[92] [b]Unilateral leukotrichia has been reported with trigeminal autonomic cephalagia, which is characterized by severe unilateral headaches lasting several minutes and is associated with hyperhidrosis or painful lacrimation.[100] *EMPD*, Extramammary Paget disease; *VKHD*, Vogt-Koyanagi-Harada disease.

reported (Supplemental Table III; available at http://www.jaad.org).[109] Depigmentation can occur spontaneously or can be precipitated by stressors, such as trauma, illness, surgery, and immunotherapy.[109-112] The natural course and prognosis of a spontaneously regressed neoplasm differs between pediatric and adult populations.

Pediatric population. Halo nevi are a common immune-mediated phenomenon that affects 1% of the population before adulthood.[113,114] The mean age of diagnosis is approximately 16 years.[109] The lesions can be solitary or multiple and are associated with vitiligo and Turner syndrome.[115-118] Complete regression of the nevus occurs in 20% to 50% of cases and leaves behind a well-defined, circular or oval, depigmented macule or patch associated with leukotrichia (Fig 11).[109,119] Rarely is the halo phenomenon associated with melanoma in children.[109] In the absence of malignant features, children with halo nevi should be provided reassurance and managed noninvasively.[113]

Adult population. Depigmentation associated with neoplastic regression is rare in older adults. Malignant melanoma should be considered in adults who present with a depigmented macule or patch and a history consistent with regression of a pigmented neoplasm.[120-125] It has been well documented that metastatic melanoma has no detectable primary site in 4% to 10% of cases.[126-128] Skin depigmentation associated with a palpable lymph node in the appropriate lymph drainage distribution is suggestive of a regressed primary melanoma[120,127,129-138] (Fig 12). The evaluation and management of such cases is complex and primarily anecdotal (Supplemental Fig 1; available at http://www.jaad.org). Depigmentation at the site of a

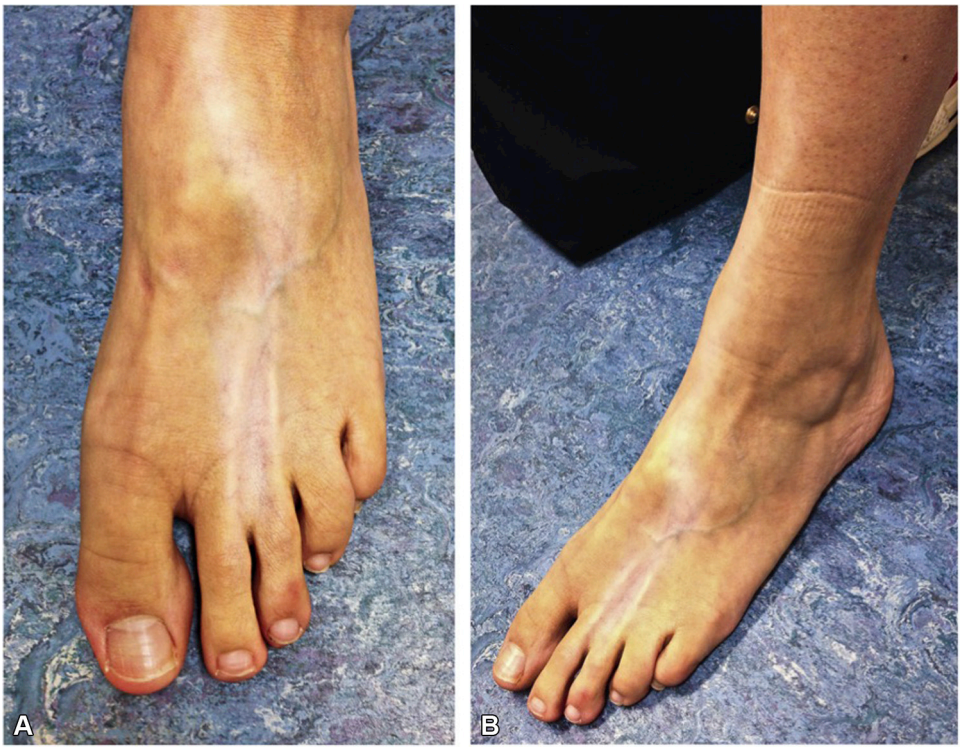

Fig 10. Adverse reaction to corticosteroid injection. Skin depigmentation along lymph vessels of the lower leg following local corticosteroid injection for interdigital neuroma. (Reprinted from van Vendeloo and Ettema[107] with permission from Elsevier.)

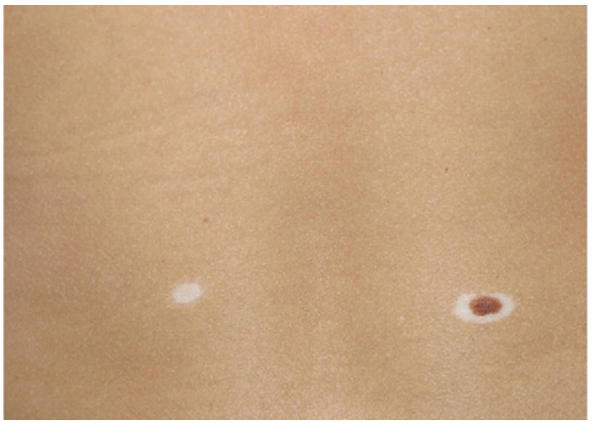

Fig 11. Halo nevi. Typical halo nevus adjacent to a depigmented macula after complete regression of the nevus. (Reprinted from Mollet et al[120] with permission from Elsevier.)

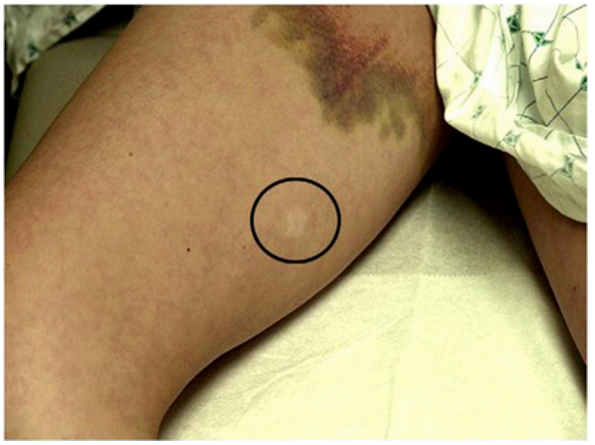

Fig 12. Primary regressed melanoma. (Reprinted from High et al[121] with permission from Elsevier.) The proposed diagnostic criteria for a completely regressed melanoma is included in Supplemental Table IV; available at http://www.jaad.org

melanocytic lesion in adults therefore warrants careful history and examination and appropriate work-up.

Other considerations

Key points

- **Depigmentation of the foreskin with dyspareunia is highly suggestive of lichen sclerosus**
- **Localized depigmentation in the genital region can be the earliest sign of extramammary Paget disease or its recurrence**
- **Obtaining a biopsy specimen may be required to establish a diagnosis of depigmented extramammary Paget disease or lichen sclerosus and to rule out squamous cell carcinoma**

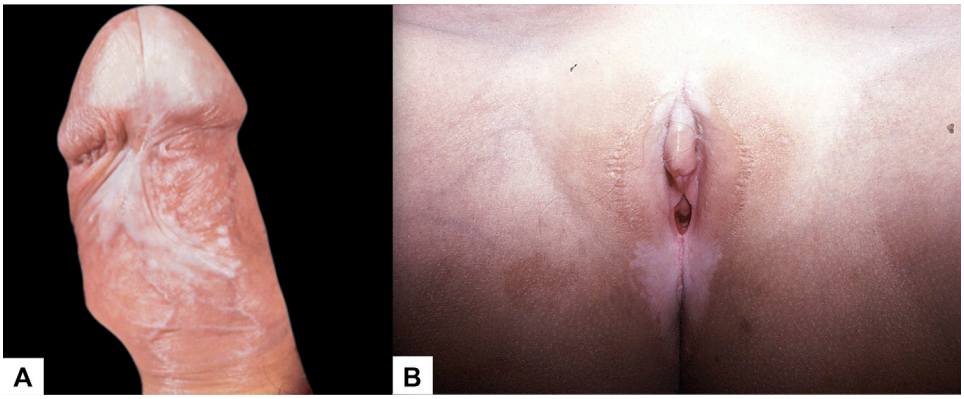

Fig 13. Genital lichen sclerosus (LS). **A,** Depigmentation and scarring of the frenulum resulting in a propensity for bleeding during sexual intercourse. **B,** Chalky white, pruritic, patches that are classical of genital LS. (**A**, Reprinted from Goldsmith et al[142] with permission from McGraw-Hill Education. Copyright McGraw-Hill Education. **B**, Reprinted from Ruiz-Maldonado[169] with permission from Elsevier.)

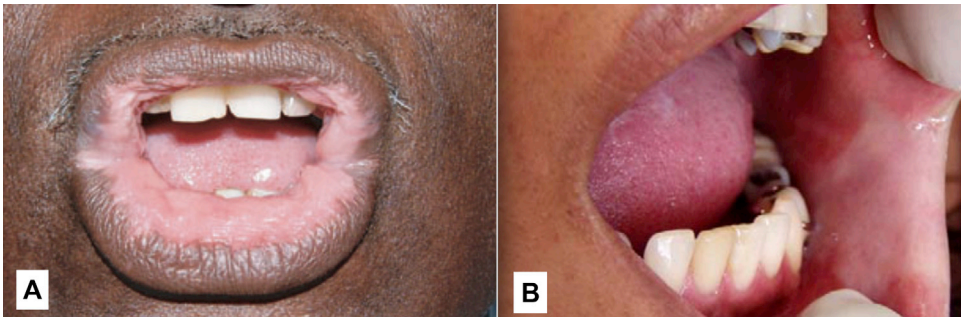

Fig 14. Oral lichen sclerosus. Diffuse vitiliginoid lichen sclerosus of (**A**) both lips and (**B**) an irregular white patch involving the buccal mucosa. (**A**, Reprinted from Attili and Attili[159] with permission of John Wiley and Sons. **B**, Reprinted from Azevedo et al[158] with permission from Elsevier.)

Lichen sclerosus (LS) and depigmented extramammary Paget disease (EMPD) can manifest with depigmentation and should be considered in any patient with genital vitiligo-like depigmentation[139-143] (Fig 13). A biopsy specimen should be obtained when depigmented lesions are accompanied by secondary changes or if an alternative diagnosis is suspected.

LS. LS is a chronic mucocutaneous disorder of unclear etiology that is characterized by violaceous erythema and milky white depigmentation, frequently of the genitals.[144] The pathogenesis of leukoderma in LS is unclear, but it results in a decreased number of melanocytes and therefore hypomelanotic or amelanotic keratinocytes.[145] The true prevalence is unknown because the disease may be asymptomatic and underdiagnosed.[146] LS manifests with well-demarcated porcelain-white patches or plaques with irregular borders and varying degrees of sclerosis.[146,147] Trauma during masturbation, intercourse, or from repeated excoriations can lead to hyperkeratosis, painful superficial erosions, purpura, or skin fissures.[144] Pruritus, dyspareunia, and dysuria are the most commonly reported symptoms of genital LS.[144,148] Male genital LS occurs almost exclusively in uncircumcised males, involves the prepuce or the glans penis, and is often associated with phimosis, paraphimosis, or postvoid dribbling.[149-151] Extragenital manifestations are often asymptomatic and usually affect the mouth, inner thigh, neck, or trunk.[152] Oral LS frequently affects the labial mucosa, buccal mucosa, gingiva, or tongue, and sometimes causes burning, pruritus, or tightness when opening the mouth[153-160] (Fig 14). If LS is left untreated, scarring and progression to squamous cell carcinoma can occur.[160]

The management of LS should be focused on minimizing sexual and urinary dysfunction, preventing disease progression, and mitigating the risk of cancer. Ultra—high-potency topical corticosteroids are considered first-line therapy and can achieve

complete resolution of skin texture and color.[154,160,161] Male circumcision can be curative in most patients.[150,162,163] Surgical referral is necessary if male genital LS is complicated by phimosis, meatal stenosis, urethral stricture, or with symptoms refractory to medical management.[161,164] Long-term follow-up every 6 to 12 months is reasonable to monitor for symptoms requiring further intervention, such as disease recurrence, progression, or development of malignancy.

EMPD. Depigmented EMPD is a cutaneous malignancy that should be considered in older adults with progressive depigmentation isolated to the genital region.[143,165] It is likely underreported in the literature and may represent ≤30% of cases of EMPD.[166] The mechanism of depigmentation is unclear, but it does not appear to be related to postinflammatory changes or melanocyte destruction.[166] Depigmented EMPD manifests with a single or multiple well-defined depigmented patches that may develop mild central erythema.[143] In patients with an established diagnosis of EMPD, the appearance of new depigmented patches or enlargement of previous depigmented patches is concerning for recurrence and should prompt obtaining a confirmatory biopsy specimen.[166] In advanced stages, erythema in an "underpants distribution" can result from lymphatic infiltration.[147] EMPD involving the male genitalia may be associated with another underlying malignancy, and the diagnosis of EMPD should prompt an investigation for a coinciding cancer. Surgical excision or Mohs micrographic surgery is typically considered the standard of care with close clinical follow-up.[143,165-168]

In conclusion, although vitiligo is the most common of the acquired depigmented disorders, it must be carefully distinguished from other disorders of depigmentation. Understanding the clinical features that help distinguish vitiligo from other vitiliginoid conditions can lead to early diagnosis and proper management. A systematic approach to acquired disorders with depigmentation and the recognition of their key clinical features can improve diagnostic accuracy, reduce unnecessary interventions, and prevent disabling complications.

This continuing medical education series is dedicated to the inspiring child with rapidly progressing hypopigmented mycosis fungoides who had been misdiagnosed with vitiligo for many months. Despite the significant stigma associated with such a disfiguring disease, the patient had an incredibly positive attitude that was beyond inspirational.

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Answers to CME examination

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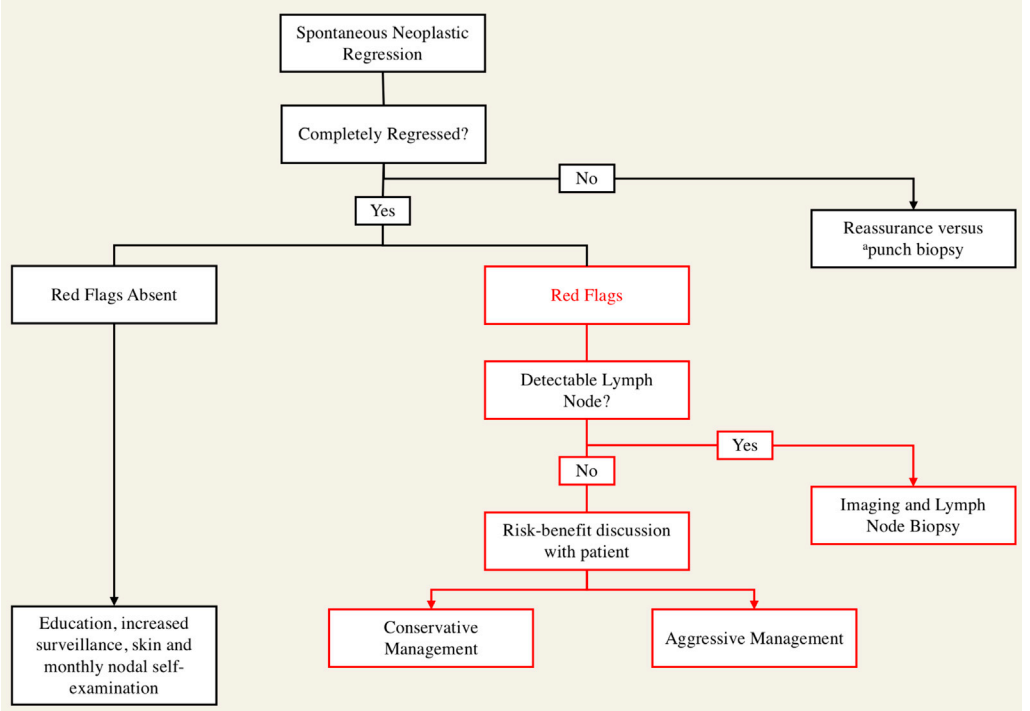

Red Flags		
History prior to regression	**Current History**	**Physical Examination**
Unstable or pigmentary changes	Multiple melanoma risk factors	[b]Palpable Lymph node
Nodular, bleeding, or ulceration	Weight loss	Concerning pigmented findings

Supplemental Fig 1. Proposed algorithm for complete regression of a pigmented lesion. The frequency of metastatic melanoma in the presence of a primary melanoma regression is unknown. The National Comprehensive Cancer Network guidelines have no recommendations on the management of a completely regressed neoplasm. Management is primarily anecdotal and differs between institutions and physicians. Conservative management includes education, increased surveillance, and self-examinations. Semiannual chest radiography, a complete blood cell count, liver function test, and lactate dehydrogenase are less invasive tools that may be of value.[S8] Many experts advocate for more aggressive management, including complete excision with 0.5- to 2-cm margins. Sentinel lymph node mapping and dissection has been suggested because removal of stage 3 disease at the microscopic stage improves survival compared with forgoing the sentinel node biopsy.[S8,S9] Complete excision and sentinel lymph node biopsy specimens that are negative may best be followed by positron emission tomography and computed tomography scans every 6 months for 2 years.[S8] The conundrum is similar to that seen with a Spitz nevus in adults. With regard to red flags, inquiring about previous photographs or asking the patient to compare the neoplasm to photographs of melanoma or benign nevi at other body sites may provide valuable information. [a]Obtaining an excisional biopsy specimen should not be recommended if melanoma is not documented histologically. Partially or completely regressed lesions are typically nondiagnostic and obtaining a punch biopsy specimen is more appropriate.[S10] [b]Targeted high-resolution ultrasonography of sentinel lymph nodes is a benign and cost-effective method for lymph node examination when a physical examination is limited because of site or body habitis. Sensitivity is highest for detecting stage IIb disease (melanoma > 4mm).[S11,S12]

Supplemental Table I. Diagnostic criteria for Vogt-Koyanagi-Harada disease*

Complete Vogt-Koyanagi-Harada disease (criteria 1-5 must be present)
- [1] No history of penetrating ocular trauma or surgery preceding the initial onset of uveitis
- [2] No clinical or laboratory evidence suggestive of other ocular disease entities
- [3] Bilateral ocular involvement (a or b must be met, depending on the stage of disease when the patient is examined)
  - a. Early manifestations of disease
    - (1) There must be evidence of a diffuse choroiditis (with or without anterior uveitis, vitreous inflammatory reaction, or optic disk hyperemia), which may manifest as 1 of the following:
      - (a) Focal areas of subretinal fluid
      - (b) Bullous serous retinal detachments
    - (2) With equivocal fundus findings; both of the following must be present as well:
      - (a) Focal areas of delay in choroidal perfusion, multifocal areas of pinpoint leakage, large placoid areas of hyperfluorescence, pooling within subretinal fluid, and optic nerve staining (listed in order of sequential appearance) by fluorescein angiography, and
      - (b) Diffuse choroidal thickening, without evidence of posterior scleritis by ultrasonography
  - b. Late manifestations of disease
    - (1) History suggestive of previous presence of findings from 3a, and either both (2) and (3) below, or multiple signs from (3):
    - (2) Ocular depigmentation (either of the following manifestations is sufficient):
      - (a) Sunset glow fundus
      - (b) Sugiura sign.
    - (3) Other ocular signs:
      - (a) Nummular chorioretinal depigmented scars
      - (b) Retinal pigment epithelium clumping or migration
      - (c) Recurrent or chronic anterior uveitis
- [4] Neurologic/auditory findings (may have resolved by time of examination)
  - (a) Meningismus (malaise, fever, headache, nausea, abdominal pain, stiffness of the neck and back, or a combination of these factors; headache alone is not sufficient to meet definition of meningismus, however)
  - (b) Tinnitus
  - (c) Cerebrospinal fluid pleocytosis
- [5] Integumentary finding (not preceding onset of central nervous system or ocular disease)
  - (a) Alopecia
  - (b) Poliosis
  - (c) Vitiligo

Incomplete Vogt-Koyanagi-Harada disease (criteria 1-3 and either 4 or 5 must be present)
- [1] No history of penetrating ocular trauma or surgery preceding the initial onset of uveitis
- [2] No clinical or laboratory evidence suggestive of other ocular disease entities
- [3] Bilateral ocular involvement
- [4] Neurologic/auditory findings; as defined for complete Vogt-Koyanagi-Harada disease above
- [5] Integumentary findings; as defined for complete Vogt-Koyanagi-Harada disease above.

Probable Vogt-Koyanagi-Harada disease (isolated ocular disease; criteria 1-3 must be present)
- [1] No history of penetrating ocular trauma or surgery preceding the initial onset of uveitis
- [2] No clinical or laboratory evidence suggestive of other ocular disease entities
- [3] Bilateral ocular involvement as defined for complete Vogt-Koyanagi-Harada disease above

*Adapted from Read et al.[S1]

Supplemental Table II. Clinical features of the various stages of Pinta disease*

	Primary	Secondary	Tertiary (late)
Time period	After 1-8 weeks' incubation	2-6 months after initial primary pinta	Years after initial infection (typically 2-5 years)
Initial symptoms	One or a few erythematous papules over uncovered skin, typically on the lower extremities	Erythematous, scaly papules termed pintids occur at distal sites from self-inoculation, typically on the extensor surfaces in an asymmetrical distribution	Bilateral symmetrical hyperpigmented, hypopigmented, or depigmented patches over bony areas (elbows, ankles, or wrists)
Progression	Over weeks, the papules coalesce and enlarges peripherally to form a large psoriasiform plaque (which may reach >20 cm in diameter)	Erythematous pintids become dyschromic, containing a hyperpigmented, violaceous, bluish-gray or black, especially at the borders. Over months, pintids involute, leaving residual hypopigmented patches	Patches may become hyperkeratotic or atrophic
Prognosis	Plaque typically completely resolves over months to years; less commonly it may persist	Pintids may recur or involute, leaving behind hypopigmented or depigmented macules or patches	Rarely resolves

*Primary phase begins with 1-3 papules at the site of inoculation.[S2] Local lymphadenopathy may occur, but constitutional symptoms are absent.[S3] No serologic test can differentiate syphilis from late pinta disease. Biopsy specimens obtained from depigmented patches in patients with tertiary pinta disease reveal epidermal atrophy and perivascular infiltrate of lymphocytes. *Treponema carateum* are seen with silver stain in the epidermis of primary and secondary pinta, but not tertiary pinta.[S3,S4] Considerable overlap occurs between primary and secondary pinta, most likely because of continuous self-inoculation.

Supplemental Table III. Spontaneous neoplastic regression: Comparison of 2 observational studies

	No halo[S5]	Halo phenomenon[S6]
Study	Prospective observational	Retrospective observational
Subjects, n	52	52
Mean age, y (range)	27 (8-67)	16 (6-52)
Distribution	Back (60%), chest (21%), abdomen (10%), and extremities (10%)	Back (60%), chest (12%), face/neck (14%), abdomen (8%), and extremities (4%)
Surrounding normal skin	Spared	Involved
Progressive depigmentation	Rapid	Slow
Complete regression,* %	37	49
Melanoma	None	1 case diagnosed

*No residual nevus was evident.

Supplemental Table IV. Simplified diagnostic criteria for completely regressed melanoma[S7]

	Criteria
1	Historical or physical evidence of a pigmented neoplasm located in a region draining a lymph node containing melanoma
2	No other primary neoplasms appreciated by history or physical examination
3	Pigmented or depigmented change at presumed primary site with histologic features consistent with regression
4	No melanoma visualized in excised lesions