Acquired disorders with hypopigmentation: A clinical approach to diagnosis and treatment

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Learning objectives
After completing this learning activity, participants should be able to list methods to aid in obtaining an appropriate history and physical examination for the hypopigmented lesion; identify the etiology of the hypopigmented lesion; and recall strategies to diagnosis of the hypopigmented lesion.

Disclosures
Editors
The editors involved with this CME activity and all content validation/peer reviewers of the journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Authors
The authors involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Planners
The planners involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s). The editorial and education staff involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Acquired hypopigmented skin changes are commonly encountered by dermatologists. Although hypopigmentation is often asymptomatic and benign, occasional serious and disabling conditions present with cutaneous hypopigmentation. A thorough history and physical examination, centered on disease distribution and morphologic findings, can aid in delineating the causes of acquired hypopigmented disorders. The second article in this 2-part continuing medical education series focuses on conditions with a hypopigmented phenotype. Early diagnosis and appropriate management of these disorders can improve a patient's quality of life, halt disease progression, and prevent irreversible disability. (J Am Acad Dermatol 2019;80:1233-50.)

Key words: arsenicosis; Bier spots; chronic arsenic exposure; copper deficiency; cutaneous T-cell lymphoid dyscrasia; drug-induced hypopigmentation; eruptive hypomelanosis; global hypopigmentation; hypopigmented mycosis fungoides; hypopigmented parapsoriasis en plaque; idiopathic guttate hypomelanosis; leprosy; leucoderma syphiliticum; leukoderma punctata; nutritional deficiencies; physiological anemic macules; pityriasis versicolor; postinflammatory hypopigmentation; progressive macular hypomelanosis; post–kala-azar dermal leishmaniasis; selenium deficiency.

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Funding sources: None.
Conflicts of interest: None disclosed.
Accepted for publication July 13, 2018.
Reprints not available from the authors.
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0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2018.07.070

Date of release: May 2019
Expiration date: May 2022

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Hypopigmentation is the loss of skin color caused by a reduction in melanin content. Although most often benign, acquired hypopigmented disorders can have significant cosmetic, psychological, economic, and societal consequences.[1,2] Investigational studies are often nondiagnostic, and therefore a systematic approach and recognition of key clinical features is critical in distinguishing between acquired hypopigmented disorders. We discuss these conditions based on lesion morphology and distribution. A simplified algorithm for classifying acquired hypopigmented disorders by distribution and primary morphology is included (Fig 1).[3-12]

DISCRETE HYPOPIGMENTED MACULES

Key points

- **The prevalence of idiopathic guttate hypomelanosis increases with age and signs of photodamage commonly accompany the macules**
- **A single session of cryotherapy is a quick and cost-effective treatment option for idiopathic guttate hypomelanosis**
- **Chronic arsenic exposure should be considered when hypopigmented macules arise on a background of diffuse hyperpigmentation**

Idiopathic guttate hypomelanosis

Idiopathic guttate hypomelanosis (IGH) is a chronic hypopigmented condition showing increasing prevalence with advancing age and is rarely seen in children and young adults (Table I).[13-15] IGH is characterized by asymptomatic, sharply demarcated, hypopigmented to depigmented macules distributed over the extremities (Fig 2, *A*).[15-19] IGH may be associated with aging, ultraviolet light exposure, trauma, or genetic factors.[7,9]

Despite its benign course, patients often seek medical care. Effective therapeutic regimens include fractional photothermolysis, excimer laser, phenol, topical 0.1% tretinoin, and cryotherapy (Supplemental Material; available at http://www.jaad.org).[20-23] A blinded randomized clinical trial found that single-session cryotherapy (5 seconds) produced clinically significant repigmentation at 4 months, consistent with previous studies.[24-26] However, cryotherapy in subjects with dark skin should be performed with caution because of the high risk for surrounding dyspigmentation. In 1 report, microinfusion of 5-fluorouracil into IGH macules using a professional tattoo machine effectively induced pigmentation (Fig 2, *B*).[19]

Leukoderma punctata

Leukoderma punctata is an IGH-like eruption that occurs as a rare complication of phototherapy in patients with chronic dermatologic disorders.[28,29] Unlike IGH, leukoderma punctata typically occurs before 40 years of age, has a predilection for females, occurs exclusively in individuals with light skin, and spontaneously resolves upon discontinuation of phototherapy.[19,28,30,31] Of note, punctate leukoderma may also occur as a delayed complication of Q-switched laser and carbon dioxide laser; however, this typically responds well to 308-nm excimer laser therapy.[32-34]

Eruptive hypomelanosis

Eruptive hypomelanosis is a benign monomorphic eruption that occurs within days to weeks after a prodromal coryzal phase.[35] Siblings may have similar symptoms, suggesting a possible infectious etiology.[36] The eruption is characterized by symmetric, discrete, uniform hypopigmented macules (often with fine powdery scale) distributed over extensor surfaces, although the trunk and face can also be involved (Fig 3).[36-38] Systemic symptoms, such as lymphadenitis and pharyngitis, may coincide. Spontaneous resolution occurs within 2 to 8 weeks; no treatment is necessary.[37,38]

Physiological anemic macules (Bier spots)

Physiological anemic macules, or Bier spots, are transient anemic macules that occur spontaneously as a result of physiologic vascular abnormalities.[39-41] They frequently present in young adults 20 to 40 years of age; cases in younger children and the elderly have been reported.[40,42] Bier spots are characterized by asymptomatic, irregularly shaped macules distributed on the extensor surfaces of the extremities (Fig 4).[40,43-50] Although most cases are idiopathic, Bier spots may be associated with lymphedema,[49] aortic abnormalities,[51,52] palmar hyperhidrosis,[48] and pregnancy.[53] They have rarely been associated with deep vein thrombosis,[54] scleroderma renal crisis,[55] and mixed cryoglobulinemia.[56] The natural history of Bier spots is unknown, but in the absence of concerning signs and symptoms patients should be reassured about their benign nature.

Chronic arsenic exposure (arsenicosis)

Discrete hypopigmented macules that present with chronic arsenic exposure (CAE) or arsenicosis can easily be mistaken for IGH, especially in tanned individuals. CAE is worth mentioning

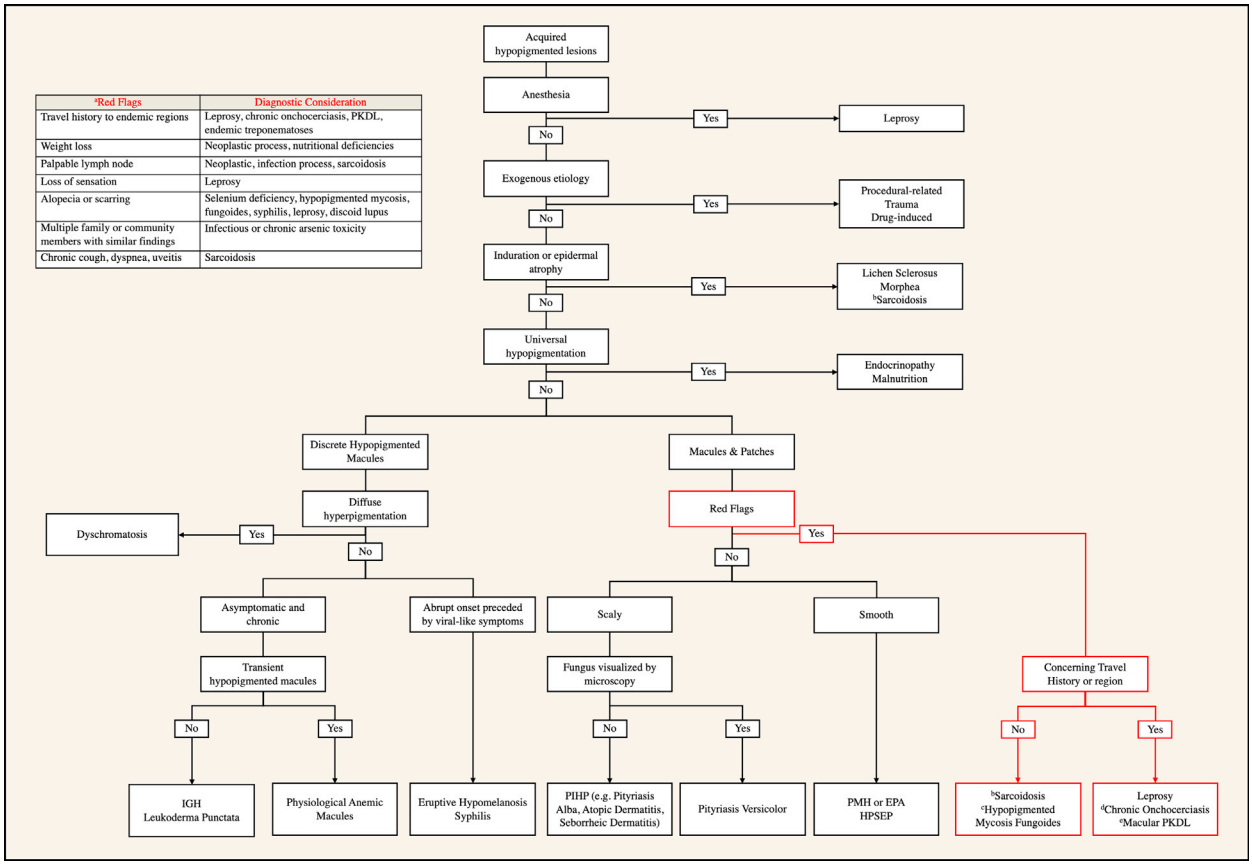

Fig 1. Proposed algorithm for approaching and classifying acquired disorders with hypopigmentation. Acquired hypopigmentation disorders are often diagnosed on clinical grounds by a thorough history and physical examination. A total body skin examination and a Wood's light examination* should be performed. The presence of epidermal atrophy or induration is suggestive of lichen sclerosus, morphea, scleroderma, tuberculoid leprosy, sarcoidosis, or cutaneous T-cell lymphoma. Weight loss, palpable lymph nodes, alopecia, or sensory loss are all red flags and suggest a more serious disease; biopsy specimens should be obtained in such cases. **Malassezia furfur* fluoresce yellow-green; however, the more common causes of pityriasis versicolor, *Malassezia globose* and *Malassezia sympodialis*, do not fluoresce.[3,4] Red fluorescence localized to the follicles is pathognomic of progressive macular hypomelanosis. [a]Failure to respond to traditional therapy is a red flag that should prompt reevaluation for another possible etiology. [b]Induration may be absent or not clinically apparent with sarcoidosis skin lesions. Common extracutaneous features include respiratory abnormalities (chronic cough, dyspnea, or chest pain), visual abnormalities (uveitis), constitutional symptoms (low-grade fever, fatigue, or weight loss), peripheral lymphadenopathy (cervical, axillary, inguinal, or epitrochlear), and hepatosplenomegaly.[5,6] [c]Hypopigmented mycosis fungoides may be mistaken for pityriasis alba, hypopigmented parapsoriasis en plaque, or progressive macular hypomelanosis. Features suggestive of hypopigmented mycosis fungoides include: progressive hypopigmentation (75%), involvement of proximal lower limbs (>80%), and patches >5 cm (>80%).[7,8] [d]Classical history includes recurrent pruritus and persistent eosinophilia. [e]Post–kala-azar dermal leishmaniasis (PDKL) can be confused for any form of leprosy. Numerous symmetrical patches involving the perioral and malar region of the face is classically seen with PDKL; in contrast, indeterminate, tuberculoid, and borderline leprosy have fewer lesions and are asymmetrically distributed.[9] In addition, neural symptoms, alopecia, nerve thickening, or loss of sweating are absent in PKDL. Similar to borderline leprosy, PKDL may also cause facial disfigurement (especially the nose).[10-12] *EPA*, Extensive pityriasis alba; *HPSEP*, hypopigmented parapsoriasis en plaque; *IGH*, idiopathic guttate hypomelanosis; *PIHP*, postinflammatory hypopigmentation; *PMH*, progressive macular hypomelanosis.

Table I. Hypopigmented dermatoses with diffuse discrete macules

	Idiopathic guttate hypomelanosis	Leukoderma punctata	Eruptive hypomelanosis	Bier spots
Epidemiology	>40 years of age	<40 years of age	≤10 years of age	≥15 years of age
Distribution	Sun-exposed areas	Site of phototherapy	Upper and lower extremities	Upper and lower extremities
Prognosis	Irreversible	Spontaneous resolution	Spontaneous resolution	Unknown
Comments	Evidence of significant photoaging	History of chronic phototherapy	Prodromal coryzal phase. Pharyngitis or lymphadenitis (cervical, axillary, or inguinal) commonly coincides	Disappears or less apparent with limb elevation, a Wood's light examination, or blanching uninvolved skin

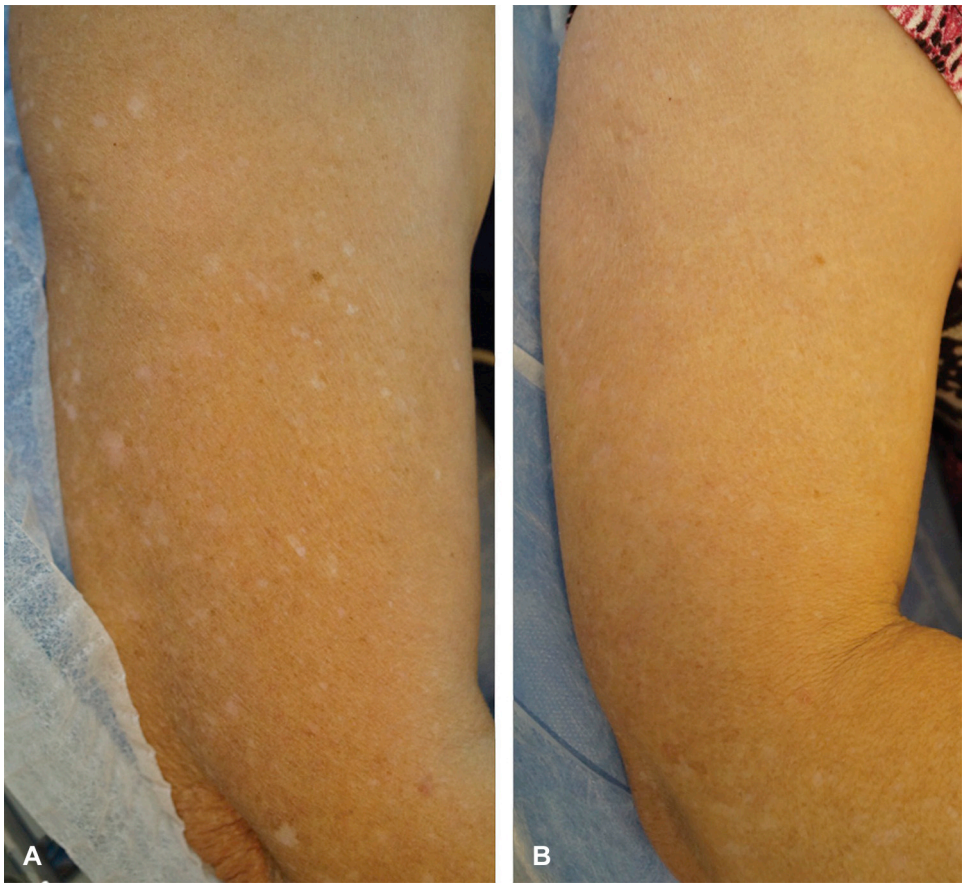

Fig 2. Idiopathic guttate hypomelanosis (IGH). (**A**) IGH before treatment and (**B**) 17 months after 2 monthly tattoo injections with 5-fluoruracil (50 mg/mL) solution. (Reprinted from Wambier et al[27] with permission from Elsevier.)

briefly because it is a global health issue[57,58] that is associated with debilitating complications.[59,60] CAE presents with discrete hypopigmented or depigmented macules on the trunk and extremities on a background of diffuse hyperpigmentation (Fig 5, *A*).[61,62] The chronicity of the associated hyperpigmentation may only be appreciated by examining previous photographs. Other skin

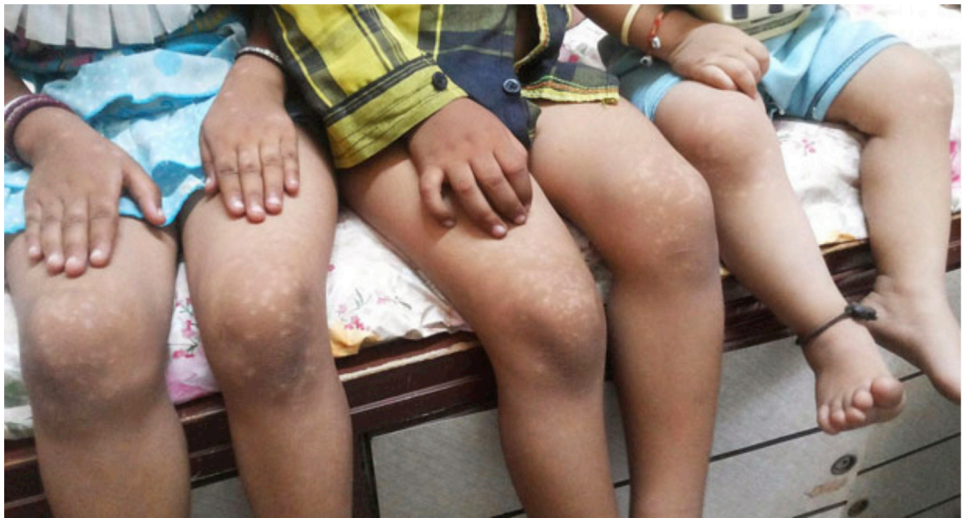

Fig 3. Eruptive hypomelanosis in a single family. Multiple symmetrical monomorphic hypopigmented macules ranging from 1.6 to 6 mm in size on the extensor aspects of the knees of the 3 patients (from left to right, patients 1, 2, and 3). Lesions were also seen on the dorsal surfaces of the wrists, hands, and fingers of patient 1. When the photograph was taken, the patients were in different stages of the exanthem, as evidenced by lichenification seen on the lesions of patient 1 but not on those of patients 2 or 3. All 3 patients were diagnosed with eruptive hypomelanosis. (Reprinted from Chuh et al,[36] with permission of John Wiley and Sons.)

findings that can coincide include palmoplantar keratosis (Fig 5, *B*), mucosal hyperpigmentation (Fig 5, *C*), and transverse leukonychia (Mees' line).[61-63] In the United States, CAE should be considered in patients using nonpublic water sources or herbal medicines and in farming communities where arsenic was used as a pesticide.[64-66] CAE begins within a few years of exposure, and cutaneous manifestations are the first sign of intoxication. Subsequent palmoplantar keratosis may occur.[67,68] Early recognition is critical because long-term complications include arsenic-induced myocardial infarction, liver damage, cognitive impairment, restrictive or obstructive pulmonary disease, cancers, adverse pregnancy outcomes, and severe peripheral vascular disease.[69-74]

VARIABLE-SIZED HYPOPIGMENTED MACULES, PATCHES, AND PLAQUES

Postinflammatory hypopigmentation

Postinflammatory hypopigmentation can result from a diverse set of dermatoses. The primary morphology of the underlying inflammatory disease often provides a straightforward diagnosis; however, low-grade inflammation may occasionally be clinically undetectable, especially in dark skin. Pityriasis alba (Fig 6, *A*) and seborrheic dermatitis (Fig 6, *B*) are common causes of postinflammatory hypopigmentation (Table II).[75,77,78,80-83] Chronic sarcoidosis should be suspected in young adults of Scandinavian or African American descent with hypopigmented macules, patches, or plaques, typically on the extremities (Fig 6, *C*), that are associated with systemic abnormalities.[5,6] Identifying the underlying etiology and controlling inflammation is the first step in management. When obtained, biopsy specimens are rarely diagnostic but can be useful in ruling out infectious or malignant mimickers.[84]

Progressive macular hypomelanosis

Key points

- **Progressive macular hypomelanosis is a common cause of hypopigmentation in adolescent females**
- **Red fluorescence, localized to the follicles under a Wood's lamp, is pathognomonic for progressive macular hypomelanosis**
- **Phototherapy is effective in inducing repigmentation; however, recurrence after treatment is common**

Progressive macular hypomelanosis (PMH) typically occurs in young females, presenting as

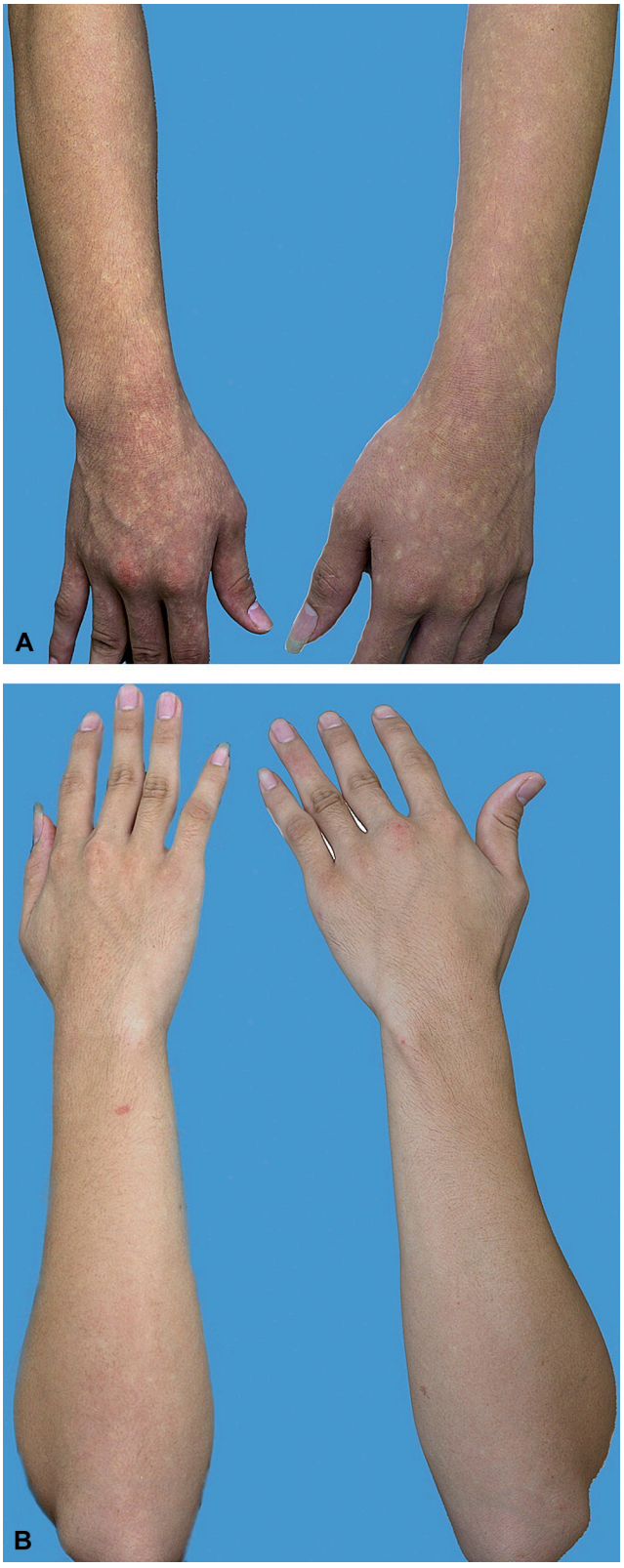

Fig 4. Bier spots. **A**, Scattered white macules on both arms and the dorsal surfaces of the hands. **B**, In the same patient, these lesions disappear when the arms are raised. (Reprinted from Fan et al,[40] with permission from Elsevier.)

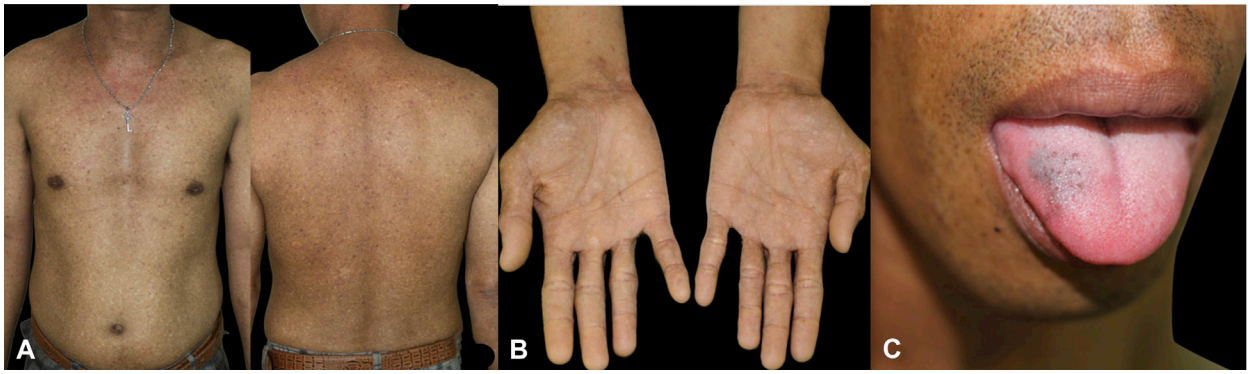

Fig 5. Chronic arsenic exposure or arsenicosis. (**A**) Speckled pigmentation, (**B**) subtle palmoplantar keratosis, and (**C**) mucosal hyperpigmentation. (Reprinted from Sy et al,[62] with permission of John Wiley and Sons.)

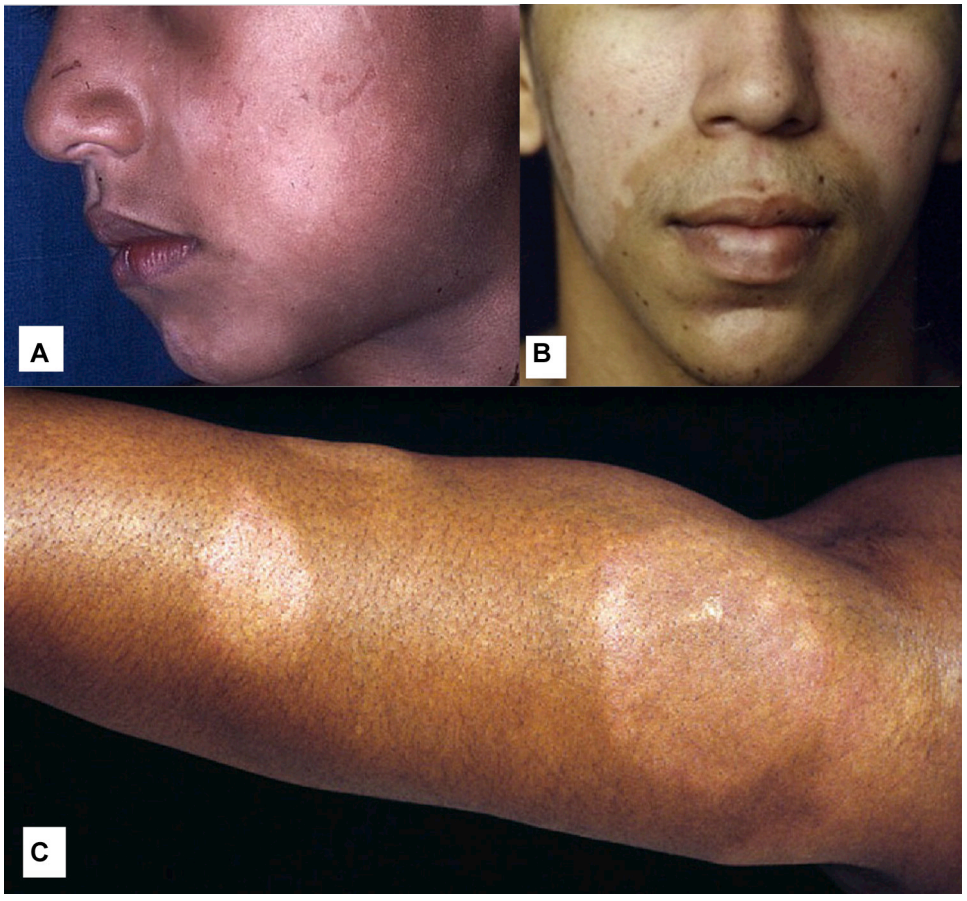

Fig 6. Postinflammatory hypopigmentation in (**A**) pityriasis alba, (**B**) seborrheic dermatitis, and (**C**) hypopigmented cutaneous sarcoidosis. (**A**, Reprinted from Ruiz-Maldonado[75]; **B**, reprinted from Talhari et al[76]; and **C**, reprinted from Fernandez-Faith and McDonnell,[5] with permission from Elsevier.)

symmetric, hypopigmented, poorly demarcated, smooth macules or patches.[85,86] A clear etiology has not been found; however, it appears that *Propionibacterium acnes* type III is involved in the formation of PMH.[87] In nearly all cases, the mid-lumbar region is involved and abdominal

Table II. Common causes of postinflammatory hypopigmentation

	Classical pityriasis alba	Pityriasis versicolor	Seborrheic dermatitis
Epidemiology	Prepubertal, with resolution after puberty	Postpubertal, rare before puberty	Infants and adults
Distribution	Face (forehead and malar ridge) and upper extremities	Trunk and upper extremities	Scalp, eyebrows, nasolabial folds, posterior auricle, and chest
Diagnosis	Clinical diagnosis; personal or family history of atopy is present in >85% of cases[77,78]	Potassium hydroxide preparation and visualization of round spores surrounding short straight rods ("spaghetti and meatballs")	Clinical diagnosis
Prognosis	Spontaneous resolution	Recurrent	Chronic
Differential*	Hypopigmented mycosis fungoides, post–kala-azar dermal leishmaniasis, and leprosy		

*Pityriasis alba is occasionally misdiagnosed as hypopigmented mycosis fungoides. Histologically, both can share similar findings. In the absence of specific findings consistent with hypopigmented mycosis fungoides, epidermotropism that is disproportionate to the degree of spongiosis suggests mycosis fungoides rather than pityriasis alba.[79]

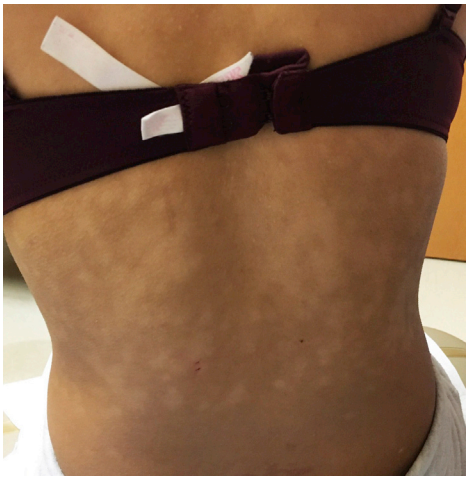

Fig 7. Progressive macular hypomelanosis: clinical view. (Reprinted from Pflederer et al,[88] with permission from Elsevier.)

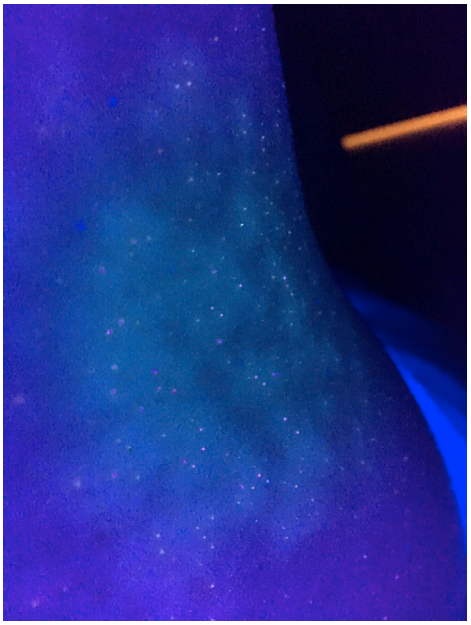

Fig 8. Progressive macular hypomelanosis: red to orange follicular fluorescence in hypopigmented skin under Wood's lamp examination. (Reprinted from Pflederer et al,[88] with permission from Elsevier.)

involvement is present in 40% of cases; rarely is the face involved (Fig 7).[86] Punctiform red to orange fluorescence localized to the follicles under a Wood's lamp is a pathognomonic finding (Fig 8) that may be a result of porphyrin production.[85,86,88,89] Cases have been reported in patients with HIV who are receiving antiretroviral therapy.[90]

Effective therapy for PMH includes phototherapy, oral isotretinoin, and combination topical benzoyl peroxide plus clindamycin (Supplemental Material; available at http://www.jaad.org).[91-97] Narrowband ultraviolet B light phototherapy induces significant repigmentation in >80% of treated patients.[81,92] PMH is typically benign and self-limiting; however, recurrence after treatment occurs in approximately 72% of patients.[81,96]

Infectious etiologies of hypopigmentation

Key points

- **Indeterminate leprosy classically presents with a smooth, well-defined hypopigmented macule or patch on the extremities or face, without sensory changes**

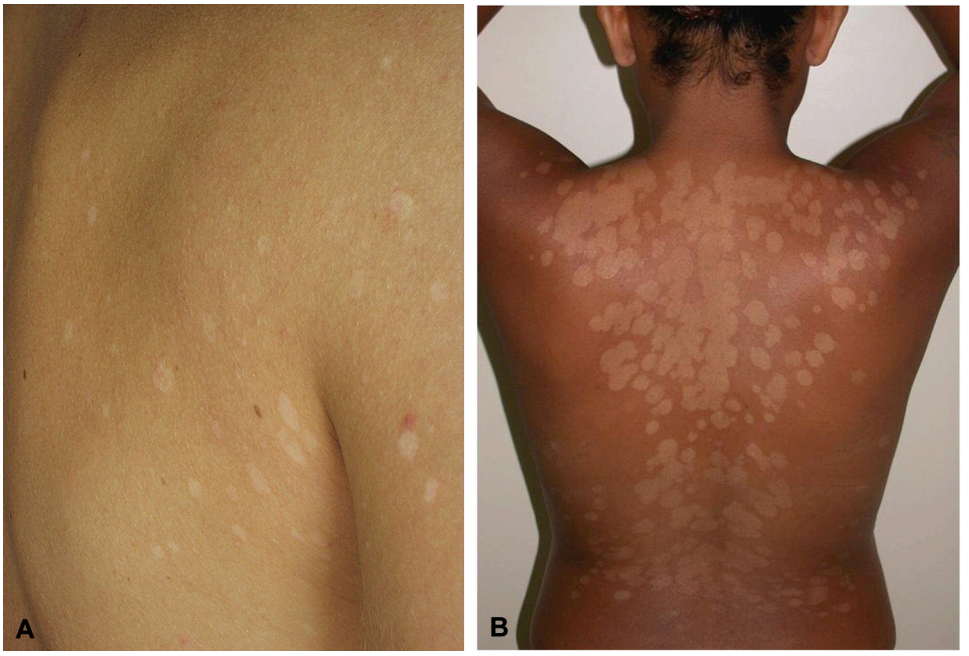

Fig 9. Hypochromic pityriasis versicolor. (**A**, Reprinted from Mollet et al[16] and **B**, reprinted from Bonifaz et al,[102] with permission from Elsevier.)

- **Macular post–kala-azar dermal leishmaniasis should be considered in patients who have traveled to East Africa or the Indian subcontinent**

Hypochromic pityriasis versicolor

Pityriasis versicolor is a superficial fungal infection caused by *Malassezia* spp. that often manifests during or after puberty. Hyperhidrosis is the most important predisposing factor; other risk factors include endocrinopathies, oral contraceptives, depressed cellular immunity, and the application of oily preparations.[98-100] Hypopigmented macules and patches with fine scale are distributed over the neck, upper trunk, and proximal upper extremities (Fig 9).[6,81,101,102] Widespread involvement of the lower extremities or face should raise concern for an immunosuppressive state such as HIV.[103]

Pityriasis versicolor is managed primarily with topical agents and sun protection.[104,105] The most effective topical agents are imidazoles and zinc pyrithione shampoos.[106] Effective oral regimens for extensive involvement include itraconazole 200 mg daily for 5 to 7 days, fluconazole 300 mg per week for 2 weeks, and pramiconazole 200 mg daily for 2 days.[106-110] Unfortunately, recurrence within 1 year occurs in 60% to 68% of patients, which may be prevented with once-a-week application of an antifungal shampoo.[106,111,112] Alternatively, prophylactic oral itraconazole 200 mg twice on 1 day per month is effective.[113] Oral ketoconazole should not be used to treat pityriasis versicolor because of the potential for fulminant hepatitis, endocrine dysfunction, and other harmful interactions.[114]

Paucibacillary leprosy

Leprosy or Hansen disease is a slowly progressive infectious disease caused by *Mycobacterium leprae*. Armadillos are the only reservoir of *M leprae*, other than humans.[115-117] In 2014, 175 cases of leprosy were reported to the National Hansen's Disease Registry, the majority of which occurred in California, Florida, Hawaii, Louisiana, New York, and Texas.[118] Worldwide, >200,000 new cases are registered annually to the World Health Organization, primarily in Southeast Asia, India, Brazil, and Indonesia.[119]

M leprae has a predilection for Schwann cells located in body sites with cooler temperatures, including the distal extremities, nose, ears, elbows, knees, and testes.[120] Numbness or hyperalgesia often precede the cutaneous manifestations of leprosy.[76,121] The earliest form, indeterminate leprosy, occurs months or years after incubation.[119] Indeterminate leprosy is characterized by ≥1 smooth, well-defined hypopigmented macules or patches with an irregular border, typically on

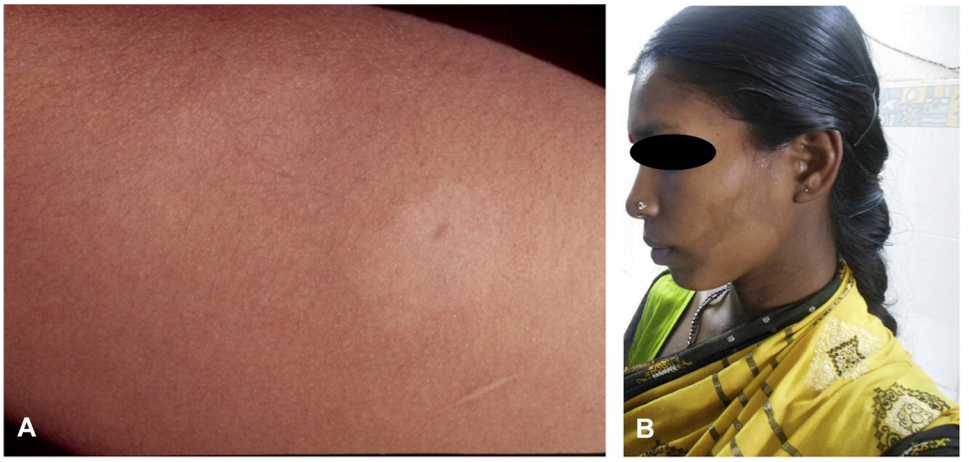

Fig 10. **A**, Indeterminate leprosy. **B**, Borderline tuberculoid leprosy with a patch over the face. (**A**, Reprinted from Talhari et al[76] and **B**, reprinted from Sarkar and Pradhan,[122] with permission from Elsevier.)

Table III. Clinical manifestations of indeterminate, tuberculoid, and borderline leprosy

	Indeterminate	Tuberculoid	Borderline
Cutaneous findings	Poorly defined, hypopigmented or erythematous macule (typically, 1 unique lesion)	Sharply demarcated macules with possible scale. May show active elevated borders (1-5 lesions)	Sharply demarcated, hypochromic, scaly plaques. May be annular
Infiltrative	No	Possible	Possible
Hypoesthetic lesion	No	Yes	Yes
Nerve involvement*	No	Occasionally enlarged nerve in the region of skin involvement	Yes
Skin smear	Negative	Positive	Positive

*Loss of temperature sensation is typically the first sign, followed by loss of light touch, pain, and pressure.

the extremities or face (Fig 10).[76,122] Associated alopecia or sensory loss is typically absent. However, loss of thermal sensation may occasionally be present.[122,123] The indeterminate form may resolve, persist, or advance to another phenotype based on the patient's immunologic response (Table III).[76] Although they can initially manifest with homogeneous hypopigmentation (Fig 11), tuberculoid and borderline leprosy are often associated with erythema and induration.[76] The National Hansen's Disease Program has established guidelines for the treatment of leprosy (Supplemental Material; available at http://www.jaad.org). Fading of erythema or repigmentation is a sign of resolution. Acute or subacute systemic reactions are common within 1 year of treatment but are rare with indeterminate leprosy (Supplemental Material; available at http://www.jaad.org).[124-127]

Macular post–kala-azar dermal leishmaniasis

Macular post–kala-azar dermal leishmaniasis (PKDL) is a chronic infection that occurs as a complication of visceral leishmaniasis. A history suggestive of visceral leishmaniasis (prolonged fever, hepatosplenomegaly, and weight loss) is reported in 90% of cases.[10,128] PKDL is endemic in East Africa and the Indian subcontinent. The clinical presentation, treatment, and prognosis of PKDL differ between regions (Supplemental Material; available at http://www.jaad.org). A macular phenotype can occur in either region but is more common with the Indian variant.[129,130] Classically, macular PKDL presents with prominent perioral hypopigmented macules that coalesce to form well demarcated, irregular patches. The patches then spread over the malar region, followed by the forehead and scalp (Fig 12). Caudal spread may occur over months to years,

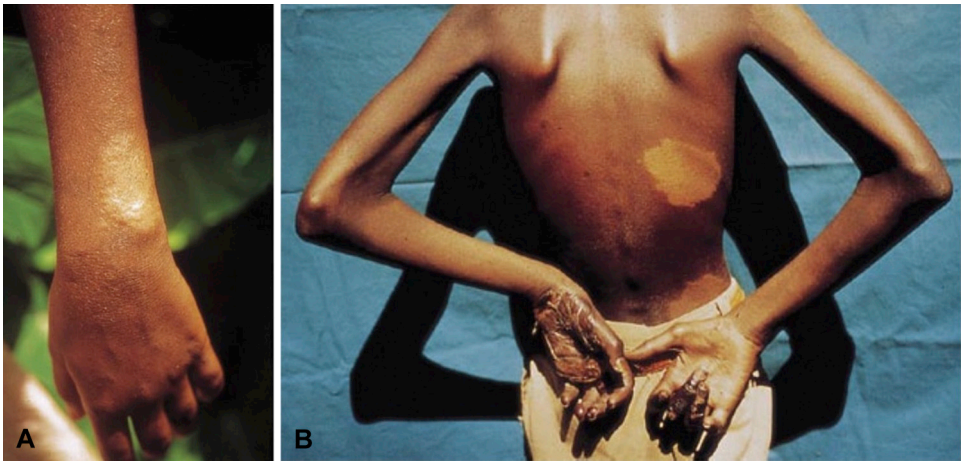

Fig 11. **A**, Tuberculoid leprosy. A typical hypopigmented, anesthetic tuberculoid lesion with a well-demarcated but active edge. **B**, Borderline tuberculoid leprosy with nerve damage. Several hypopigmented patches can be seen. This boy burned his hands as a consequence of anesthesia caused by bilateral ulnar and median nerve involvement. (Reprinted from Lockwood[9] with permission from Elsevier.)

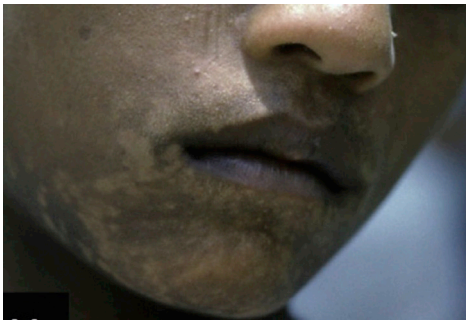

Fig 12. Macular post–kala-azar dermal leishmaniasis. (Photography courtesy of Dr Philippe Desjeux, former head of the World Health Organization's Leishmaniasis Control Programme.)

especially in young children.[11,131] Hair pigment is spared, and depigmentation is absent.[129]

Sudanese PKDL often resolves spontaneously. In contrast, PKDL on the Indian subcontinent persists without treatment. Treatment regimens include sodium stibogluconate, amphotericin B, or paromomycin (Supplemental Material; available at http://www.jaad.org).[132,133] Treatment failures and disease relapse are common and can be difficult to differentiate from delayed repigmentation. Cure is typically defined as complete resolution of lesions or repigmentation by 12 months posttreatment.[129]

Leucoderma syphiliticum

Syphilis remains prevalent in the United States and continues to be a source of morbidity and mortality.[134,135] The painless ulcer associated with primary syphilis may go unnoticed or neglected, especially when it occurs internally (eg, oral, vaginal, or anal mucosa).[136] Secondary syphilis occurs 6 to 8 weeks after primary infection, with nonspecific systemic symptoms often accompanied by a cutaneous eruption. A hypopigmented macular

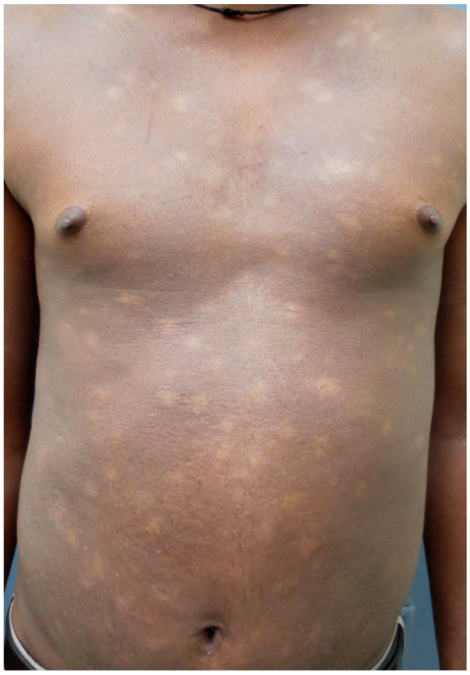

Fig 13. Secondary syphilis. (Reprinted from Uprety et al[139] with permission of John Wiley and Sons.)

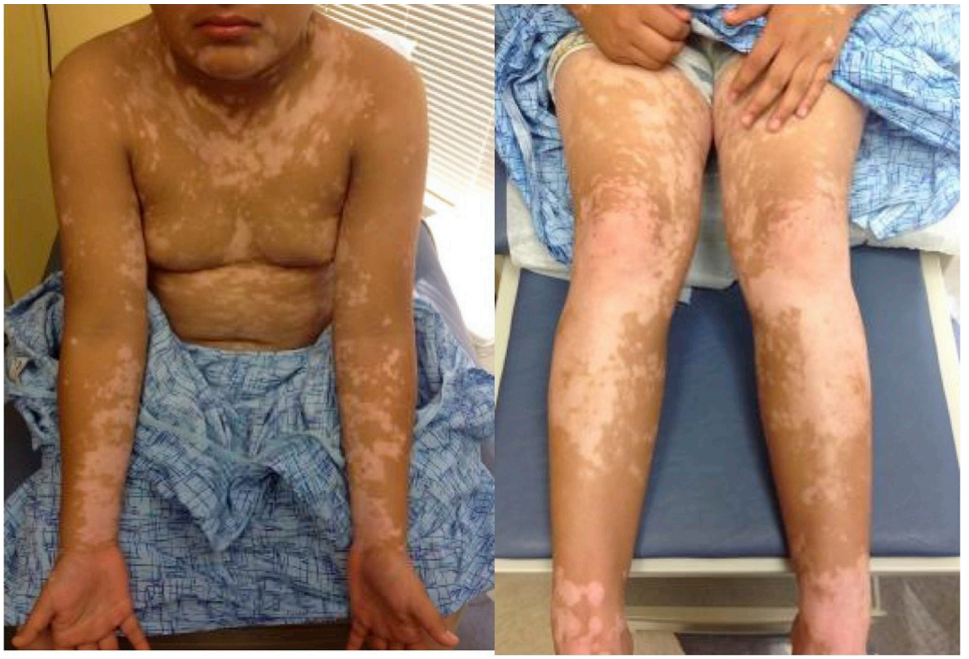

Fig 14. Hypopigmented mycosis fungoides.

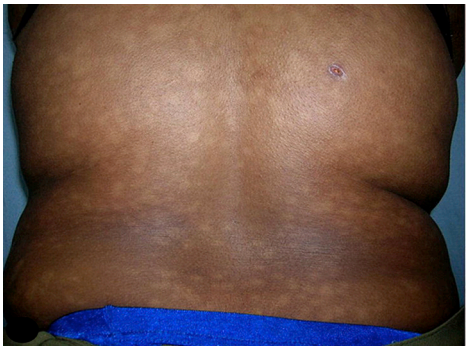

Fig 15. Hypopigmented parapsoriasis en plaque. (Reprinted from El-Darouti et al[145] with permission from Elsevier.)

eruption may be present, with or without alopecia, and can be preceded by erythema (Fig 13).[137-139] Comprehensive treatment guidelines for syphilis are available on the Centers for Disease Control and Prevention website.[140]

NEOPLASTIC ETIOLOGIES OF HYPOPIGMENTATION

Key points

- **The diagnosis of hypopigmented mycosis fungoides frequently requires obtaining multiple biopsy specimens**
- **Hypopigmented mycosis fungoides follows a waxing and waning course, often requiring long-term treatment**
- **Hypopigmented parapsoriasis en plaque is managed similarly to hypopigmented mycosis fungoides and frequently resolves within 2 years**

Hypopigmented mycosis fungoides

Hypopigmented mycosis fungoides (HMF) is insidious in onset with a predilection for darkly pigmented skin.[141] In contrast to classic MF, HMF often presents in children or young adults.[142-144] HMF is characterized by hypopigmented or depigmented patches, frequently with scale, and classically involving the trunk and inner thighs (Fig 14).[145] Nearly all cases involve the hip/gluteal region.[146-148] The diagnosis frequently requires obtaining multiple biopsy specimens, which should be obtained from steroid-naïve sites. In the absence of tumor, lymphadenopathy, or systemic symptoms, no additional diagnostic imaging is required.[149]

HMF has a 20-year survival rate of 98% and responds well to therapy.[150-152] Effective treatments include topical nitrogen mustard, topical carmustine, topical and oral bexarotene, topical corticosteroids, methotrexate, pralatrexate, and light therapy (Supplemental Material; available at

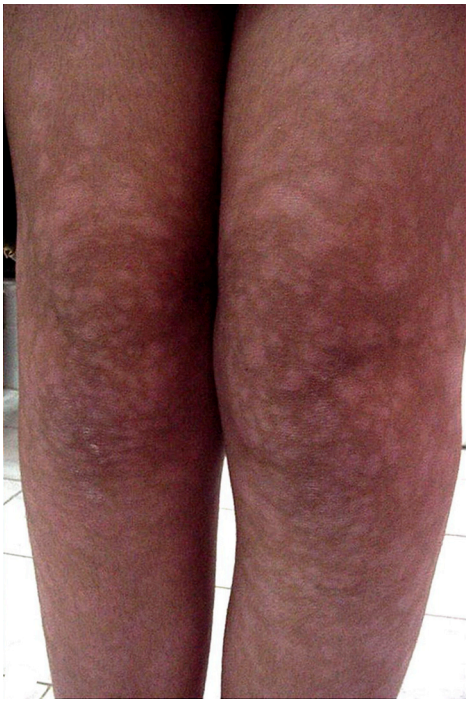

Fig 16. Hypopigmented parapsoriasis en plaque. Digitiform or "finger-like" projections. Reprinted from J Am Acad Dermatol. (Reprinted from El-Darouti et al[145] with permission from Elsevier.)

http://www.jaad.org).[150,153-158] Repigmentation signifies clinical and histopathologic resolution.[7,151] Unfortunately, HMF follows a waxing and waning course and requires long-term treatment. Recurrence after complete resolution commonly occurs.[149,150,152]

Cutaneous T-cell lymphoid dyscrasia and hypopigmented parapsoriasis en plaque

Cutaneous T-cell lymphoid dyscrasia encompasses a group of skin disorders including parapsoriasis and hypopigmented interface variants. Hypopigmented parapsoriasis en plaque (PSEP) presents with smooth, oval, or round hypopigmented macules or patches in photoprotected regions (Fig 15); 70% have digitiform extensions (Fig 16).[145] Hypopigmented PSEP and cutaneous T-cell lymphoid dyscrasia are managed similarly to HMF. PSEP treated with narrowband ultraviolet B light phototherapy frequently resolves within 2 years; only 14% of cases progress to HMF.[140,145,146,159]

Other considerations

Key points

- **Tyrosine kinase inhibitors may cause hypopigmented skin changes; repigmentation often occurs once the agent is discontinued**

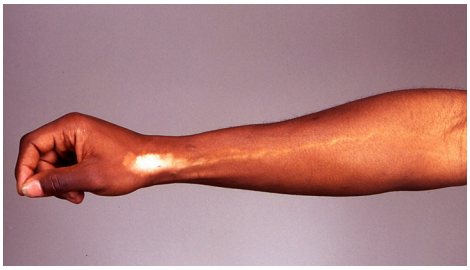

Fig 17. Adverse reaction to corticosteroid injection. Progressive hypopigmentation over the anatomic snuff box after 2 peritendinous triamcinolone injections performed 6 months apart. Complete spontaneous repigmentation occurred 7 months after the initial injection. (Reprinted from Saour et al,[175] with permission from Elsevier.)

- **Corticosteroid injections can cause localized hypopigmentation that may expand along a lymphatic or venous distribution**

Exogenous causes of pigment loss include medications, cryotherapy, chemicals, burns, and laser interventions.[160-165] Hypopigmentation of the skin after therapy with tyrosine kinase inhibitors (pazopanib, imatinib mesylate, dasatinib, or sunitinib) occurs frequently; repigmentation occurs once tyrosine kinase inhibitors are discontinued.[166-174] These patients have an impaired response to tanning and should be cautioned about sunburns, regardless of skin type.[167] Local hypopigmentation can occur a few weeks after a local corticosteroid injection, with or without epidermal atrophy, and may progress by linear extension along a lymphatic or venous distribution (Fig 17).[175-184] Spontaneous resolution occurs within 6 to 9 months.[175] Hypopigmentation has been reported from corticosteroid inhaler application to skin as a competition among friends.[185-187]

GENERALIZED (GLOBAL) HYPOPIGMENTATION

Endocrinopathies and nutritional deficiencies

Endocrinopathies (hypogonadism or hypopituitarism) and nutritional deficiencies (copper and selenium) are rare acquired causes of global hypopigmentation in the United States. The loss of pituitary hormones frequently causes nonspecific symptoms, such as fatigue, decreased libido, and menstrual or sexual dysfunction.[188,189] Copper deficiency can occur years after gastric bypass surgery and is often complicated by pancytopenia, an unsteady gait, and distal paresthesia.[190-192] Early signs of selenium deficiency are xerosis,

hypopigmentation, alopecia, leukotrichia, and leukonychia; muscle pain and weakness are also common. Severe selenium deficiency can lead to cardiac arrhythmia or cardiomyopathy.[193-196] Early identification and intervention prevents associated complications.

In conclusion, a systematic approach to acquired hypopigmented disorders helps guide the clinician in identifying possible underlying etiologies. The diagnosis of such disorders is often established with a thorough history and physical examination. Early diagnosis and appropriate management reduce disease burden and improve patients' quality of life.

We thank Dr Anne Burdick for her input into the leprosy section of this article and Dr Lindsay C. Strowd for her input into the initial draft and the hypopigmented mycosis fungoides section of this article.

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Supplemental Table I. Clinical studies for the treatment of idiopathic guttate hypomelanosis

Study, year	Size, n	Summary
Gordon et al,[S1] 2017	6 (all females)	Single-blinded trial with 6 subjects treated with excimer laser for 12-week treatment regimen; each patient had 5 IGH lesions selected on each leg (1 for treatment and the other for control); at week 12, on average, a moderate improvement (between 50-75% repigmentation) was noted in the treated lesions and was statistically significant
Laosakul et al,[S2] 2016	101 (macules)	58 control subjects; 43 single sessions of 5-second cryotherapy; at 4 months, 82% vs 2% (control) had >75% improvement as measured by colorimeter from baseline
Rerknimitr et al,[S3] 2015	30	120 macules: 60 control macules (sham treatment) and 60 treated macules (treated with fractional photothermolysis); improvement measured by physician improvement score seen in 83% of macules (treatment) vs 18% (control), $P < .05$
Ravikiran et al,[S4] 2014	20	139 macules treated with spot peel (88% phenol); repigmentation occurred in 64% of macules, measured objectively
Rerknimitr et al,[S5] 2013	26	Topical 0.1% tacrolimus ointment improves IGH measured by colorimeter at 6 months ($P = .019$); no statistical improvement of clinical assessment after 6 months
Kumarasinghe et al,[S6] 2004	4	3-5 sec of light cryotherapy results in improvement at 6 weeks
Pagnoni et al,[S7] 1999	4	Topical 0.1% tretinoin daily results in significant improvement in pigmentation, elasticity, and glyphic markings after 4 months

MEDLINE was searched for articles that included "progressive macular hypomelanosis" in the title and that were published in the last 10 years; 18 search results were returned. Of 18, 7 pertaining to treatment were included.
IGH, Idiopathic guttate hypomelanosis.

Supplemental Table II. Clinical studies for the treatment of progressive macular hypomelanosis

Study, year	Size, n	Evidence
Thng et al,[S8] 2016	108	108 identified through retrospective analysis; 40 opted for no treatment (23% had spontaneous resolution, mean = 10 months); 36 treated with topical clindamycin and/or benzoyl peroxide (38% had "good" repigmentation; mean = 9 months), but "good was not defined (no relapse); 32 treated with NBUVB twice weekly, >90% achieved >80% repigmentation (recurrence rate 6%, mean = 10 months)
Kim et al,[S9] 2012	Letter to editor	Oral isotretinoin 10 mg daily showed improvement with maintained remission at 10 months
Kim et al,[S10] 2012	23	NBUVB once or twice weekly, maintaining, MED resulted in repigmentation of affected areas, with minimum risk for recurrence
Cavalcanti et al,[S11] 2011	13 (1 lost to follow-up)	Lymecycline 300 mg daily plus 5% benzoyl peroxide at night for 12 weeks; 10/12 subjects had 90% improvement
Santos et al,[S12] 2011	23	Topical benzoyl peroxide 5% and clindamycin 1% plus sunlight was significantly superior to sunlight alone ($P = .003$)
Sim et al,[S13] 2011	10	NBUVB twice a week for 8 weeks has equal efficacy to NBUVB plus topical clindamycin/benzoyl peroxide combination
Duarte et al,[S14] 2010	84	PUVA (methoxsalen at 0.4 mg/kg) and NBUVB are effective treatment options; NBUVB compared with PUVA shows equal efficacy ($P < .05$)
Relyveld et al,[S15] 2006	45	Benzoyl peroxide 5% hydrogel, clindamycin 1% lotion, and UVA phototherapy is superior to fluticasone cream plus UVA

MEDLINE was searched for articles that included "progressive macular hypomelanosis" in the title and that were published in the last 10 years; 34 search results were returned. Of 34, 8 pertaining to treatment were identified and included.
MED, Minimum effective dose; *NBUVB*, narrowband ultraviolet B light phototherapy; *PUVA*, psoralen plus ultraviolet A light phototherapy.

Supplemental Table III. Clinical studies for the treatment of post-kala-azar dermal leishmaniasis

Study, year	Size, n (country)	Summary
Abongomera et al,[S16] 2016	422 (South Sudan)	Severe or complicated PKDL subjects: 343 received SSG (20 mg/kg/day) IM, 79 received combination SSG/PM (20 mg/kg/day; 15 mg sulphate/kg/day) IM for 17 days; cure rate was 97% vs 90% (monotherapy); $P = .02$
Ghosh et al,[S17] 2015	27 (India)	Single-arm, open-label miltefosine oral daily for 16 weeks: 9 lost to follow-up because of side effects (abdominal pain, nausea, vomiting), 7 completed 12 weeks, 3 had relapse; 11 completed 16 weeks, no relapse
Sundar et al,[S18] 2015	33 (India)	Slit skin smear or PCR-proven PKDL ≥10 years of age were administered oral miltefosine (100 mg if ≥25 kg; 50 mg <25; 2.5 mg/kg for children) daily for 12 weeks; follow-up at 1 year: 3 withdrew from the study, 1 stopped treatment because of adverse effects; 28 cured, defined by complete disappearance of lesions; 1 failed treatment
Sundar et al,[S19] 2013	36 (India)	Open-label, randomized multicenter trial with 100 mg/day of miltefosine for 8 or 12 weeks, outcomes measured at 12 months; both groups achieved similar cure rates >75% in the intended-to-treat analysis

MEDLINE was searched for articles containing key terms pertaining to leishmaniasis in the title and published in the past 5 years.
IM, Intramuscular; *PCR*, polymerase chain reaction; *PKDL*, post-kala-azar dermal leishmaniasis; *PM*, paromomycin; *SSG*, sodium stibogluconate.

Supplemental Table IV. Clinical studies for the treatment of hypopigmented mycosis fungoides

Studies	Size, n	Summary	Recurrence
Gameiro et al,[S20] 2014	1	8-year-old male treated with NBUVB phototherapy 3 sessions/week with complete clinical response after 30 sessions (cumulative dose of 41.7 J/cm^2)	No recurrence reported at 10 months
Shehab et al,[S21] 2014	1	NBUVB 3 times/week with complete resolution after 6 months. Maintained on NBUVB weekly for 3 months, followed by reduction to once weekly	Not reported
Juhas et al,[S22] 2013	1	Topical steroids plus PUVA 3 times weekly with topical steroids for maintenance therapy	None
Kanokrungsee et al,[S23] 2012	11	NBUVB twice weekly, starting dose of 40% of MED with adjustments based on previous sessions	Recurrence in 3 subjects (median 10 months)
Ozcan et al,[S24] 2008	1	Stage IA HMF treated with NBUV 4 times/week for 6 months	No recurrence at 1 year
Roupe et al,[S25] 2005	1	9-year-old female treated with UVA1-light (340-400 nm) for 1 year	No recurrence at 4 years
Akaraphanth et al,[S26] 2000	9	8 (stage IA), 1 (stage IB), 8 treated with PUVA 2-3 times/week; 3 treated with topical mechlorethamine; 1 failed to tolerate treatment, and another developed contact dermatitis; third patient had a partial response; all recurrence responded rapidly to UV therapy	Recurrence in 8/9 subjects; remission lasted as long as 3 years
Lambroza et al,[S27] 1995	7	6/7 successfully treated with PUVA with complete remission; 1 case of stage IB HMF treated with whole-body electron beam therapy (3600 rad, 6 MeV, 100-200 rad/session) with adjuvant single dose doxorubicin (30 mg/m^2) intravenously followed by 6 cycles of oral cyclophosphamide (100 mg/m^2/day) given 14 days on/14 days off for 6 months	Case 2: recurrence after 2 months

MEDLINE was searched for articles published in the last 5 years that contained key medical subject headings, including "hypopigmentation, lymphoma, T-cell, and therapy." No clinical trials were found, only case reports and case series. Of 54 articles returned in the search, 7 were accessible and included treatment outcomes.

HMF, Hypopigmented mycosis fungoides *MED*, minimum effective dose; *NBUVB*, narrowband ultraviolet B light phototherapy; *PUVA*, psoralen plus ultraviolet A light phototherapy.

Supplemental Table V. NHDP treatment recommendations and alternatives for paucibacillary leprosy[S28]

First-line regimens		
Population	**Regimen***	**Duration†**
Pediatric population	Dapsone 1 mg/kg/day; rifampin 10 mg/kg/day (do not exceed 600 mg)	1 year
Pregnant and adult population	Dapsone 100 mg/day; rifampin 600 mg/day	1 year

Alternative options‡		
Replaced	**Alternative**	**Comment**
Dapsone	Minocycline 100 mg/day	Contraindicated in pregnancy and children
Any	Clarithromycin 500 mg/day	Increased risk of death in patients with stable coronary heart disease[S29]
Any	Clofazimine 50 mg/day	Requires the physician register as an investigator under the NHDP investigational new drug
Clofazimine	Ofloxacin 400 mg/day	Avoid in children

NHDP, National Hansen's Disease Program.

*Only 1-year treatment is required; bacilli may be present in the skin for >1 year; however, this is not clinically significant.

†Dapsone may cause agranulocytosis and hemolytic anemia. Rifampin may cause renal or hepatic dysfunction or bone marrow suppression.

‡A large clinical trial involving 268 subjects with leprosy and 1-5 skin lesions (paucibacillary leprosy) demonstrated similar cure rates with either monthly (rifampin, ofloxacin, and minocycline) or daily (dapsone and rifampin) over 6 months.[S30]

Supplemental Table VI. Features of type 1 reaction and type 2 reaction, also known as reversal reaction or erythema nodoum leprosum, respectively

	Type 1 reaction	Type 2 reaction
Association	Borderline or tuberculoid	Borderline or lepromatous
Pathophysiology	Type IV hypersensitivity reaction	Type III hypersensitivity reaction
Cutaneous manifestations	Previous lesions swell and become erythematous	Crops of painful subcutaneous nodules
Clinical features[S31-S35]	Hand and food edema; nerves may become tender or palpable; previous peripheral neuropathy may worsen	Flu-like symptoms of high-grade fever, anorexia, and arthralgias*
Complications	Neuritis†	Iridocyclitis, neuritis, orchitis, and glomerulonephritis‡
Management	If neuritis or ulcers develop, long-term treatment is required; low-dose prednisone or prednisolone plus steroid-sparing agents[S35-S38]	Prednisone daily, tapered over 4 weeks; steroid-sparing agents effective include clofazimine, thalidomide, and methotrexate[S39,S40]

*Serology may reveal anemia, neutrophilic leukocytosis, and albuminuria.[S37]

†Patients may complain of dropping items, difficulty walking, and facial or peripheral pain. Neuritis may be silent, making it difficult to detect during follow-up.

‡Iridocyclitis is a rare complication, but is a medical emergency requiring immediate ophthalmologic consultation alongside atropine and corticosteroid eye drops.[S38]

Supplemental Table VII. Comparison of post-kala-azar dermal leishmaniasis by region[S41,S42]

	East Africa	Indian subcontinent
Endemic regions	Sudan, South Sudan, and Ethiopia	India, Bangladesh, and Nepal
Incidence after VL infection*	60%	10%
Time to onset of PKDL	0-6 months	2- to 3-year intervals
Mucosal and genital lesions	Never	Possible
Lymphadenopathy	Common	Rare
Para-kala-azar dermal leishmaniasis†	Possible	Rarely
Prognosis	Spontaneous resolution within 1 year‡	Requires treatment
Extracutaneous complications	Uveitis, conjunctivitis, and blindness	

PKDL, Post-kala-azar dermal leishmaniasis; *VL*, visceral leishmaniasis.

*The risk of developing PKDL may be much lower in patients treated with miltefosine, paromomycin, or combination therapy for VL.[S43-S45]

†In 15% of cases, systemic symptoms, such as malaise, fever, and splenomegaly, may coincide with PKDL—called para-kala-azar dermal leishmaniasis.[S42]

‡Sudanese PKDL resolves spontaneously within 90 days without treatment; disease lasting >6 months is considered chronic and requires treatment.[S46]

Supplemental Table VIII. Post-kala-azar dermal leishmaniasis treatment options in order of most commonly used

East Africa	Indian subcontinent
• Pentavalent antimonial 20 mg Sb^{5+}/kg IM or IV for 17-60 days PLUS • Paromomycin 15 mg in 11 mg base/kg/day IM for 17 days	• Amphotericin B deoxycholate 1 mg/kg/day infusion, up to 60-80 doses over 4 months*
• Pentavalent antimonial 20 mg Sb^{5+}/kg IM or IV for 30-60 days	• Miltefosine 50 mg (<25 kg) or 100 mg (>25 kg) oral/day for 12 weeks†‡
• Liposomal amphotericin B 2.5 mg/kg/day by infusion for 20 days	• Liposomal amphotericin B* 5 mg/kg/day infusion 2 times per week for 3 weeks for a total dose of 30 mg/kg‡
• Miltefosine 100 mg/day for 28 days in patients coinfected with HIV	

Adopted from the World Health Organization report of a consultative meeting, Kolkata, India.[S42] Treatment of Sudanese PKDL is often unnecessary because the majority of cases resolve spontaneously.[S41,S47] The exceptions include: subjects with persistent (>6 months) disfiguring PKDL, associated anterior uveitis, or concomitant mucosal PKDL require treatment.[S48] In contrast to Sudanese PKDL, the World Health Organization recommends treatment for all cases of Indian subcontinent PKDL.

*Potassium supplementation is recommended for this regimen given in a patient's diet (for all patients) or through intravenous infusion (for those with proven severe hypokalemia). To prevent serious adverse effects caused by hypokalemia, patients should be monitored for any related signs or symptoms. Hypokalemia should be suspected in all patients with general weakness, nausea, myalgia, muscle weakness, or cramps occurring during or after treatment.

†Because the safety of courses of miltefosine lasting longer than 4 weeks has not been evaluated, all patients should be closely monitored for side effects.

‡Recently, an open-label trial demonstrated a significant reduction in relapse of PKDL in patients treated with oral miltefosine for 16 weeks compared with 12 weeks.[S17] Unfortunately, associated nausea, vomiting, and abdominal pain may limit compliance.[S17] A study looking at the safety and efficacy of miltefosine for the treatment of PKDL in children is currently underway (clinical trial number NCT02193022).[S49]