Vitiligo: Pathogenesis, clinical features, and diagnosis

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Literature review current through: Apr 2022. | **This topic last updated:** May 17, 2022.

INTRODUCTION

Vitiligo is a relatively common acquired disorder of pigmentation characterized by the development of well-defined, depigmented macules on the skin. Biopsies of lesional skin reveal a loss of epidermal melanocytes [1-4]. Lesions may occur in a localized or generalized distribution and may coalesce into large, depigmented areas. Given the contrast between the white areas and normal skin, the disease is most disfiguring in individuals with darkly pigmented skin and has a profound impact on the quality of life of both children and adults [5,6]. Patients with vitiligo often experience stigmatization, social isolation, and low self-esteem [7-10].

This topic will review the pathogenesis, classification, clinical manifestations, and diagnosis of vitiligo. The management and prognosis of vitiligo are discussed separately. Other pigmentation disorders are also discussed separately.

- (See "Vitiligo: Management and prognosis".)
- (See "Acquired hypopigmentation disorders other than vitiligo".)
- (See "Acquired hyperpigmentation disorders".)
- (See "Melasma: Management".)
- (See "Postinflammatory hyperpigmentation".)

EPIDEMIOLOGY

Vitiligo is the most frequent cause of skin depigmentation [2-4,11]. Estimated prevalence rates range from 0.1 to 2 percent in both adults and children [12-16]. In a population-based, online survey of over 40,000 adults in the United States, the estimated point prevalence of vitiligo was 1.38 percent (self-reported) and 0.76 percent (clinician adjudicated) [17].

Vitiligo affects equally males and females, without racial, ethnic, or socio-economic predilections [13]. It may appear at any age from early childhood to late adulthood, with peak incidences in the second and third decade of life [18]. Approximately one-third of patients with vitiligo are children, and 70 to 80 percent of adult patients develop vitiligo prior to age 30 years [2].

ETIOLOGY

The etiology of vitiligo is unknown. Patients commonly attribute the onset of their disease to specific triggering events such as physical injury or illness, sunburn, emotional stress, or pregnancy, but there are no data supporting a causative role for these factors. The frequency of comorbid autoimmune diseases is significantly elevated in patients with vitiligo and in their first-degree relatives, suggesting an autoimmune etiology for this disorder [13].

Recipients of hematopoietic stem cell transplantation (HSCT) appear to have an increased risk of developing vitiligo [19,20]. In a Korean nationwide population study including 2747 HSCT recipients and 8241 controls, HSCT recipients had a three-fold increased risk of having vitiligo compared with controls (odds ratio 3.13, 95% CI 1.86-5.27) [21]. Allogeneic HSCT and bone marrow-sourced stem cells were independently associated with the development of vitiligo after HSCT. The pathogenetic mechanisms underlying the development of vitiligo in HSCT recipients are unclear. They may include adoptive transfer of vitiligo from donor [22], immunosuppression associated with preparative regimens, or chronic graft-versus-host disease [23].

PATHOGENESIS

Multiple theories have been proposed for melanocyte destruction in vitiligo. These include genetic, autoimmune, neural, biochemical, oxidative stress, viral infection, and melanocyte detachment mechanisms. Although the autoimmune and oxidative stress theories are best supported by research data, none of the proposed theories are in themselves sufficient to explain the diverse vitiligo phenotypes [3,24,25]. The so-called "convergence theory" suggests

that multiple mechanisms may contribute to the disappearance of melanocytes in vitiliginous skin and that vitiligo may indeed represent a disease spectrum [26].

Genetics — Family clustering of vitiligo suggests a genetic basis for the disease [13,27]. Genetic studies indicate a non-Mendelian, multifactorial, polygenic inheritance pattern [28-30]. Twenty-five to 50 percent of persons with vitiligo have affected relatives [13,27]. A survey conducted among 2624 patients with vitiligo from North America and the United Kingdom found a 6 percent prevalence of vitiligo in siblings of patients with vitiligo [13]. In this cohort, the concordance in monozygotic twins was only 23 percent, suggesting that nongenetic factors and/or environmental triggers play a role in the pathogenesis of the disease.

Genetic studies have identified approximately 36 susceptibility loci for nonsegmental vitiligo [31]. The majority of the susceptibility genes encode immunoregulatory proteins, whereas several encode melanocyte proteins. Multiple studies have also implicated human leukocyte antigen loci in vitiligo, including A2, DR4, DR7, DQ7, DR1, B13, DQW3, CW6, and A30 [25,28,29,32,33]. In genome-wide association studies, several genes with known associations with other autoimmune disorders were identified as potential susceptibility loci for generalized vitiligo, including *PTPN22*, *LPP*, *IL2RA*, *UBASH3A*, *C1QTNF6*, and genes encoding major histocompatibility complex (MHC) I and MHC II molecules [16,18,24,25,34-37].

However, there is significant genetic heterogeneity in different ethnic groups. A genome-wide linkage study performed in 71 White multiplex families with vitiligo from North America and the United Kingdom found highly significant linkage to the autoimmune disease susceptibility locus *AIS1* on chromosome 1p31, suggesting that *AIS1* is a major susceptibility locus [30]. The corresponding gene was subsequently identified as *FOXD3* [38]. Genetic studies in Chinese families have shown linkage evidence to chromosome 4q13-q21 [39].

Other candidate genes for vitiligo susceptibility include the catalase gene, vitiligo-associated protein 1 on chromosome 2p16, and the guanosine triphosphate cyclohydrolase I gene [24,28,29]. The *NALP1* gene on chromosome 17p13, encoding the NACHT leucine-rich repeat protein 1, a regulator of the innate immune system, has been linked to vitiligo-associated multiple autoimmune disease, a group of diseases including various combinations of vitiligo, autoimmune thyroid disease, and other autoimmune and autoinflammatory syndromes [40].

Autoimmunity — Historically, vitiligo has been associated with several autoimmune diseases, including Hashimoto's thyroiditis, Graves' disease, type 1 diabetes mellitus, alopecia areata, pernicious anemia, rheumatoid arthritis, autoimmune polyglandular syndrome, and psoriasis [18,25,41,42]. A survey in North America and the United Kingdom found that approximately 20

percent of 2624 vitiligo probands had a history of autoimmune thyroid disease compared with 2 percent of the general population [13].

Many humoral and cell-mediated immune aberrations have been reported in patients with vitiligo, including an increased frequency of organ-specific autoantibodies, such as antithyroglobulin, antithyroid peroxidase, antiparietal cells, and antinuclear antibodies [43,44]. The presence of antibodies to surface and cytoplasmic melanocyte antigens in the sera of patients with vitiligo lends additional support to the autoimmune pathogenesis of this disease [45-47]. These antibodies can induce the destruction of melanocytes grown in culture by complement-mediated lysis and antibody-dependent cellular cytotoxicity [45,46]. In addition, melanocyte antibodies, when passively administered to nude mice grafted with human skin, have a destructive effect on melanocytes within the skin graft [48].

Studies also suggest that cytotoxic T lymphocytes may play a significant role in melanocyte destruction in vitiligo [49]. Numerous activated cytotoxic T lymphocytes have been reported in the perilesional area of the vitiliginous skin, often in apposition to disappearing melanocytes [50]. These infiltrating lymphocytes are predominantly cytotoxic $CD8^+$ lymphocytes that express the skin homing receptor cutaneous leucocyte-associated antigen receptor. Moreover, purified $CD8^+$ T cells isolated from lesional skin of patients with vitiligo can induce melanocyte apoptosis in autologous nonlesional skin explants [51,52].

Multiple cytokines have also been implicated in the destruction of melanocytes in vitiligo. Several studies have documented increased expression of tumor necrosis factor-alpha, interferon-gamma, interleukin (IL) 10, and IL-17 in lesional skin of patients [3]. Investigations suggest that the interferon gamma-induced chemokine CXCL-10 is a key mediator of melanocyte destruction [53].

Melanocyte self-destruction hypothesis — The self-destruction hypothesis proposes that melanocytes may be destroyed from an intrinsic increased sensitivity to oxidative stress arising from toxic phenolic compounds formed during the synthesis of melanin [54]. This hypothesis is supported by the observation that a number of ubiquitous compounds containing catechols, phenols, and sulfhydryls (eg, industrial chemicals, cleaning agents, some hair dyes) can induce hypopigmentation, depigmentation, or both. Possible mechanisms for altered pigment production by these compounds include melanocyte destruction via free-radical formation, inhibition of tyrosinase activity, and interference with the production or transfer of melanosomes [55]. Additional data suggest that phenols can activate the unfolded protein response in melanocytes, causing induction of factor X-box binding protein 1, which leads to the production of IL-6 and IL-8 and recruitment of immune cells to the affected areas [51].

Oxidative stress hypothesis — Several studies suggest that oxidative stress may be the initial event in the destruction of melanocytes [56,57]. An imbalance of intracellular redox status and a significant depletion of enzymatic and nonenzymatic antioxidants have been demonstrated in the epidermis of patients with active vitiligo [58]. Low catalase and glutathione levels (but increased superoxide dismutase and xanthine oxidase levels) have also been found in the peripheral blood of patients with vitiligo [55].

Defective recycling of 6-tetrahydrobiopterin (6BH4), increased production of hydrogen peroxide, and decreased catalase levels have also been found in lesional skin of patients with vitiligo [56,57,59]. The altered tetrahydrobiopterin homeostasis may result in increased levels of toxic metabolites (eg, 6BH4 and 7-tetrahydrobiopterin) and hydrogen peroxide and reduced levels of catalase, a key enzyme involved in hydrogen peroxide removal, which may further contribute to cell death [60].

Oxidative stress may also contribute to melanocyte destruction in susceptible individuals via activation of the innate immune response [2,3]. Reactive oxygen species can act as danger signals and activate pattern recognition receptors to initiate inflammation, with local recruitment of innate immune cell populations, such as macrophages, natural killer cells, and inflammatory dendritic cells [51].

Neural hypothesis — The neural hypothesis posits that nerve endings situated near pigment cells may secrete a neurochemical mediator that is cytotoxic to the melanocytes [25]. This hypothesis is supported by the observation that the distribution of the depigmented areas in segmental vitiligo is related to dermatomes, even though the segments are almost never strictly dermatomal [25,61]. Moreover, vitiligo has been reported following neurologic disorders such as viral encephalitis, multiple sclerosis with Horner syndrome, and peripheral nerve injury [25,62]. Laboratory findings also support the neural hypothesis. Axon degeneration has been seen in dermal nerves of vitiliginous skin but not in dermal nerves of normal skin [63]. Immunohistochemistry studies of nerve endings in skin surrounding vitiligo lesions have shown abnormalities in the expression of nerve growth factors and neuropeptides [64]. Blood levels of certain neuropeptides are increased among patients with active vitiligo [65,66].

Melanocytorrhagy hypothesis — This theory proposes that melanocyte loss in vitiligo is secondary to chronic melanocyte detachment from the basement membrane. Causes include trauma, reactive oxygen species, autoimmune defects, and abnormal synthesis of extracellular matrix proteins leading to impaired cell adhesion [54,67].

CLINICAL FEATURES

General features — Vitiligo typically presents with asymptomatic depigmented macules and patches, milk or chalk white in color, that lack clinical signs of inflammation (picture 1). Severe sunburn, pregnancy, skin trauma, and/or emotional stress may precede the disease onset [68]. Lesions can appear at any age and anywhere on the body, with a predilection for the face and areas around the orifices, genitals, and hands. They vary in size from a few millimeters to many centimeters and usually have convex borders well-demarcated from the surrounding normal skin.

Vitiligo may show more than one color shade. Trichrome lesions are characterized by zones of white, light-brown, and normal skin color and are most often observed in individuals with darkly pigmented skin. Quadrichrome lesions may have a perifollicular or marginal hyperpigmentation, whereas pentachrome lesions present also a blue hue [12,69]. Another clinical variant is the so-called vitiligo ponctué, which exhibits tiny, confetti-like depigmented macules.

Koebner phenomenon — Repeated mechanical trauma (friction) and other types of physical trauma (eg, scratching, chronic pressure, or cuts) along with allergic or irritant contact reactions may trigger vitiligo on areas such as the neck, elbows, and ankles [70]. This is known as the Koebner phenomenon, also called "isomorphic response," which describes the development of skin disease in sites of skin trauma. The Koebner phenomenon has been reported in 20 to 60 percent of patients with vitiligo [70].

Associated findings — Depigmented hairs are often present in lesional skin. While such hairs indicate a reduction or loss of the follicular reservoir for repigmentation, their presence does not invariably preclude the repigmentation of a lesion (picture 2). Poliosis, a decrease or absence of melanin or color in head hair, eyebrows, and/or eyelashes, may also be a manifestation of vitiligo (picture 3) [62]. Premature graying of scalp hair may occur in patients with vitiligo and in their families.

Halo nevi, characterized by a surrounding area of depigmentation (picture 4A), have been identified in 6 to 26 percent of children with nonsegmental vitiligo and may portend the development of generalized vitiligo [71-74]. (See "Acquired melanocytic nevi (moles)", section on 'Halo nevi'.)

Based upon the analysis of a large series of patients with vitiligo, two age-related clinical phenotypes have been identified [75]. Patients with childhood onset (before age 12 years) often have a family history of vitiligo and/or premature hair graying, associated halo nevi, and Koebner phenomenon, and report previous episodes of depigmentation and repigmentation. In contrast, patients with vitiligo onset during adolescence or early adulthood frequently report

a personal or family history of autoimmune diseases and have disease localized to the face and/or acral sites [75].

Clinical classification — A detailed classification scheme for vitiligo was proposed in 2012 by the Vitiligo Global Issues Consensus Conference [11]. Vitiligo is classified in two broad categories: nonsegmental vitiligo (the most common) and segmental vitiligo (table 1). Nonsegmental vitiligo is further divided into subtypes based upon the distribution of skin lesions (ie, generalized, acral or acrofacial, mucosal, localized, universal, and mixed pattern). Rare subtypes are included in the undetermined/unclassified group.

Nonsegmental vitiligo — Nonsegmental vitiligo includes the generalized, acrofacial or acral, mucosal, and universal subtypes (table 1). Generalized and acral or acrofacial vitiligo are most common:

- **Generalized vitiligo** – Generalized vitiligo is characterized by bilateral, often symmetrical, depigmented macules or patches occurring in a random distribution over multiple areas of the body surface. Generalized vitiligo may begin in childhood or early adulthood and often occurs at sites subjected to pressure, friction, and/or trauma. Depigmented patches are common on the face, trunk, and extremities.

- **Acrofacial or acral vitiligo** – Acrofacial or acral vitiligo consists of depigmented macules confined to the distal extremities and/or the face (picture 5). It may later include other body sites, resulting in typical generalized vitiligo [2,11]. A subcategory of the acrofacial type is the lip-tip variety, in which lesions are confined to the cutaneous lips (picture 6) and distal tips of the digits.

- **Mucosal vitiligo** – Mucosal vitiligo typically involves the oral and/or genital mucosa. It may occur in the context of generalized vitiligo or as an isolated manifestation [76].

- **Universal vitiligo** – Universal vitiligo refers to complete or nearly complete depigmentation of the skin. Some skin areas and hairs may be partially spared. Universal vitiligo usually results from progression of generalized vitiligo.

- **Vitiligo minor** – Vitiligo minor or hypochromic vitiligo is characterized by an incomplete loss of pigmentation resulting in areas of the skin that are paler than the surrounding skin. Vitiligo minor is more frequently seen in individuals with darkly pigmented skin [77].

Segmental vitiligo — Segmental vitiligo typically occurs in a dermatomal or quasi-dermatomal pattern, most frequently along the distribution of the trigeminal nerve (picture 7). While being the least common type of vitiligo, segmental vitiligo begins during

childhood or early adulthood in most cases [8,78]. In a series of 925 patients with segmental vitiligo from a Chinese Han population, 59 percent developed segmental vitiligo before age 20, and 80 percent developed segmental vitiligo before age 30 [79]. The areas of depigmentation usually stabilize within a year and rarely spread beyond the affected dermatome. There is early involvement of hair follicles (leukotrichia), with histologic evidence of destruction of the follicular melanocyte reservoir.

Plurisegmental vitiligo may have multiple segments involved, either unilaterally or bilaterally. The onset of different segmental lesions may or may not be simultaneous. Plurisegmental vitiligo can be differentiated from bilateral nonsegmental vitiligo by the restriction of the lesions to identifiable segments, presence of leukotrichia, and protracted course.

Ocular involvement — Melanocytes of the eye, ear, and leptomeninges also may be affected in vitiligo [80,81]. Depigmented areas of the retinal pigment epithelium and choroid have been reported in 30 to 40 percent of patients [82-84]. These asymptomatic lesions do not interfere with visual acuity.

ASSOCIATED DISORDERS

Autoimmune diseases — Vitiligo is frequently associated with autoimmune thyroid disease and other autoimmune or immune-mediated diseases, including alopecia areata, psoriasis, type 1 diabetes, rheumatoid arthritis, inflammatory bowel disease, pernicious anemia, linear morphea, myasthenia gravis, discoid and systemic lupus erythematosus, and Sjögren syndrome [13,85-90]. Patients with comorbid autoimmune diseases are more likely to have generalized vitiligo compared with patients without associated diseases [88]:

- In a review of 2441 adult patients (mean age 51 years) with vitiligo, 12 percent had an autoimmune thyroid disorder, 8 percent psoriasis, 3 percent rheumatoid arthritis, and 2 percent inflammatory bowel disease [86]. Approximately 40 percent of patients had elevated antinuclear antibodies and 50 percent elevated antibodies to thyroid peroxidase.

- In another retrospective study of 1098 patients with vitiligo, approximately 20 percent had one or more comorbid autoimmune diseases, most commonly thyroid disease (12 percent) [88]. Alopecia areata was the second most common comorbid disease (2.8 percent), followed by psoriasis, inflammatory bowel disease, and type 1 diabetes mellitus.

Vitiligo may also be a clinical feature of polyglandular autoimmune syndromes, in particular autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED; polyglandular

autoimmune syndrome type 1 [PAS1]) and Addison's disease with autoimmune thyroid disease (Schmidt's syndrome) [91,92].

Genetic syndromes — Vitiligo is associated with several genetic disorders, which include:

- **Vogt-Koyanagi-Harada syndrome** – Vogt-Koyanagi-Harada syndrome is a rare multisystem disease characterized by chronic uveitis, poliosis (decrease or absence of melanin or color in head hair), alopecia, dysacousia, vitiligo, and signs of meningeal irritation [93]. Vogt-Koyanagi-Harada syndrome usually manifests in the third decade of life and, although reported in all ethnic groups, tends to be more severe in populations with darkly pigmented skin. (See "Uveitis: Etiology, clinical manifestations, and diagnosis", section on 'Systemic inflammatory diseases'.)

- **Alezzandrini syndrome** – Alezzandrini syndrome is a rare condition characterized by unilateral facial vitiligo, unilateral retinal degeneration, poliosis (decrease or absence of melanin or color in head hair), and hearing loss [94,95].

- **Kabuki syndrome** – Kabuki syndrome is a rare multisystem disorder caused by mutations in the *KMT2D* and *KDMA6* genes and characterized by developmental delay, mild to moderate intellectual disability, skeletal and visceral anomalies, dermatoglyphic anomalies, and a characteristic facial dysmorphism [96]. Some of these patients also have immunologic defects and/or autoimmune diseases, including vitiligo [97-99].

Melanoma — Rarely, hypopigmented patches resembling vitiligo may precede a diagnosis of cutaneous melanoma [100-102]. The presence of vitiligo-like depigmentation in patients with melanoma is thought to be a marker of an immune response against the tumor and may be an indicator of favorable prognosis in advanced disease [44,103].

Psychosocial issues — Vitiligo may be a psychologically devastating disorder, with a major impact on the patient's self-image and self-esteem [9,104]. The mental health and emotional burden of vitiligo is more severe in female patients and in individuals with darkly pigmented skin, in whom the lesions of vitiligo are more prominent [2,105-107]. A 2018 systematic review and meta-analysis of 25 studies including over 2000 patients with vitiligo found a pooled prevalence of depression of 29 percent (95% CI 21-38 percent), based on depression-specific questionnaires [108].

In some countries, the confusion with leprosy is an important cause of social stigma and isolation. Children with vitiligo may suffer from severe psychologic trauma, resulting in impaired social and emotional development and compromised quality of life later in adulthood [109,110].

CLINICAL COURSE

The clinical course of vitiligo is unpredictable. Lesions can remain stable or progress slowly for years [2]. In most cases, the extent and distribution of lesions change during the course of a person's lifetime by centrifugal expansion of current lesions and/or the appearance of new lesions. Progression is more common in patients who have a family history of nonsegmental vitiligo, a longer duration of disease, Koebner phenomenon, and mucosal involvement, but the rate of progression in the individual patient is unpredictable [2,12,14].

Flare-ups are common and may be separated by stable periods. Stable vitiligo is most common in children and adolescents, regardless of ethnicity and skin type [78]. Lesions can be considered stable if no change is detected by serial photography in a 12-month period [11].

DIAGNOSIS

Clinical — The diagnosis of vitiligo is in most cases straightforward, based upon the clinical finding of acquired, discrete, well-demarcated, uniformly white macules with convex borders surrounded by normal skin in the absence of inflammation or textural changes [12,14,111]. Elements of history that are helpful for the diagnosis include:

- Age at onset of lesions
- Factors or events that may have preceded onset
- Symptoms associated with the lesions
- Progression or spread of lesions
- Changes observed in lesions over time
- Presence of concomitant diseases
- Current medications
- Occupational history/exposure to chemicals
- Family history of vitiligo and autoimmune diseases

Diagnostic aids — The diagnosis of vitiligo may be facilitated by the use of a Wood's lamp (a handheld device emitting ultraviolet A light at approximately a 365 nm wavelength), especially in individuals with pale skin [14]. Under the Wood's light, the depigmented areas emit a bright blue-white fluorescence and appear sharply demarcated [12]. (See "Office-based dermatologic diagnostic procedures", section on 'Wood's lamp examination (black light)'.)

Dermoscopy may be helpful in differentiating evolving vitiligo patches from other diseases with similar patterns of hypopigmentation. On dermoscopy, vitiliginous macules typically show

residual perifollicular pigmentation and telangiectasia, which are absent in other hypopigmentation disorders [112,113].

Pathology — A skin biopsy is not routinely required for the diagnosis of vitiligo. However, the examination of a skin biopsy that includes the lesion border and an adjacent, uninvolved area of skin, along with careful clinicopathologic correlation, may be helpful to establish the diagnosis in patients with hypopigmented or depigmented lesions of questionable etiology. On histology, vitiligo reveals complete loss of melanin pigment in the epidermis and absence of melanocytes, with occasional lymphocytes at the advancing border of the lesions (picture 8). Other findings include vacuolar degeneration of basal and parabasal keratinocytes, focal spongiosis, and a dermal lymphohistiocytic infiltrate at the dermoepidermal interface, especially in perilesional skin of actively spreading vitiligo [114,115]. Immunohistochemical staining shows a preponderance of $CD8^+$ T lymphocytes in the inflammatory infiltrate [116].

Laboratory studies — Given the relatively high frequency of the association of vitiligo with autoimmune thyroid disease, it is reasonable to screen all patients with vitiligo, and especially those with generalized disease and extensive involvement of the body surface, for thyroid function [87,117,118]. (See 'Associated disorders' above.)

European guidelines based upon expert consensus recommend the assessment of thyroid function (thyroid-stimulating hormone, antithyroperoxidase, and antithyroglobulin antibodies) in all patients with vitiligo [54]. They also recommend the measurement of additional autoantibodies only if the patient's history, family history, or physical examination suggests other autoimmune diseases. Low-titer antinuclear antibody positivity may not preclude the use of phototherapy and may not be associated with increased risk of phototoxic reactions [119]. (See "Clinical significance of antinuclear antibody staining patterns and associated autoantibodies".)

DIFFERENTIAL DIAGNOSIS

Many common and uncommon disorders are characterized by areas of depigmentation that may mimic vitiligo [10,14,120-125]. To differentiate vitiligo from mimickers, it is important to evaluate the skin texture and whether there is or is not complete depigmentation. Vitiligo is **not** associated with scaling or textural changes, although some patients may rarely develop inflammatory vitiligo characterized by raised, erythematous borders.

Conditions that are frequently confused with vitiligo include (see "Acquired hypopigmentation disorders other than vitiligo"):

- **Nevus depigmentosus** – Nevus depigmentosus (picture 9) is a circumscribed, segmental area of depigmentation or hypopigmentation usually present at birth or detected in the first years of life [14]. The lesion shows little change over time, although it may enlarge as the patient grows. Nevus depigmentosus is a form of cutaneous mosaicism, caused by an altered clone of melanocytes with a decreased ability to produce melanin, abnormal melanosomes, and inability to transfer pigment to keratinocytes [126,127]. When seen under a Wood's lamp, the contrast between lesional and normal skin is less marked than in vitiligo [12,14].

- **Pityriasis alba** – Pityriasis alba commonly affects children and is considered a component of the spectrum of atopic dermatitis. It is characterized by hypopigmented, mildly scaling patches common on sun-exposed areas (picture 10A-B). Such patches usually clear with or without treatment with low-potency corticosteroids. (See "Acquired hypopigmentation disorders other than vitiligo", section on 'Pityriasis alba'.)

- **Idiopathic guttate hypomelanosis** – Idiopathic guttate hypomelanosis is a common disorder characterized by multiple small, asymptomatic, porcelain-white macules primarily on the sun-exposed areas of the limbs (picture 11A-B) [69,128]. Its incidence increases with age and is seen in up to 80 percent of patients over the age of 70 years. Once present, lesions do not change in size or coalesce. Melanocytes are present, although they may be reduced in number. (See "Acquired hypopigmentation disorders other than vitiligo", section on 'Idiopathic guttate hypomelanosis'.)

- **Tinea (pityriasis) versicolor** – Tinea versicolor is a superficial yeast infection that can cause loss of pigment. It is caused by saprophytic, lipid-dependent yeasts in the genus *Malassezia* (*Pityrosporum*). It presents as pale macules typically located on the upper trunk and chest, with a fine, dry surface scale (picture 12) [12,47]. Involved areas often fluoresce a golden yellow when examined under a Wood's lamp [12]. (See "Tinea versicolor (pityriasis versicolor)".)

- **Halo nevus** – Halo nevus, also called Sutton nevus, is a melanocytic nevus surrounded by a round or oval halo of depigmentation (picture 4A-B) [129]. This pigment loss often heralds the spontaneous regression of the central nevus. A single circular lesion on the trunk of a young person may represent a resolving halo nevus. (See "Acquired melanocytic nevi (moles)", section on 'Halo nevi'.)

- **Piebaldism** – Piebaldism (MIM #172800) is a rare autosomal-dominant disorder presenting at birth with anterior midline depigmentation and a white forelock (poliosis) (picture 13). Irregular depigmented areas may also be present on the trunk and

extremities. Rarely, lesions show a hyperpigmented border [121]. Distribution on the forehead and chin supports the diagnosis.

- **Progressive macular hypomelanosis** – Progressive macular hypomelanosis is characterized by nonscaling hypopigmented patches of the trunk caused by *Cutibacterium* (formerly *Propionibacterium*) *acnes* (picture 14). The condition is most common in young patients. (See "Acquired hypopigmentation disorders other than vitiligo", section on 'Progressive macular hypomelanosis'.)

- **Lichen sclerosus** – Lichen sclerosus is an uncommon condition characterized by atrophic, white, firm lesions that most commonly affect the anogenital area but may also affect extragenital skin. Vitiligo affecting only the genital area can be difficult to differentiate from lichen sclerosus, which can also coexist with vitiligo. A skin biopsy may be necessary to clarify the diagnosis in difficult cases. (See "Extragenital lichen sclerosus" and "Vulvar lichen sclerosus".)

- **Chemical leukoderma** – Chemical leukoderma initially presents with depigmentation at the contact area but may later spread to other areas (picture 15). Occupational hazards for chemical leukoderma include phenolic-catecholic derivatives including monobenzyl ether of hydroquinone (monobenzone), para tertiary butyl catechol, para tertiary butyl phenol, paraphenylenediamine and amino phenol, para tertiary amyl phenol, hydroquinone, and monomethyl ether [14].

  Leukoderma secondary to chemicals can also be induced by dyes, perfumes, detergents, cleansers, insecticides, rubber condoms, rubber slippers, black socks and shoes, eyeliner, lip liner, lipstick, toothpaste, antiseptics with phenolic derivatives, mercuric iodide-containing "germicidal" soap, and arsenic-containing compounds [130,131]. In 2013, thousands of patients in Japan developed depigmentation after using a brightening cream containing rhododendrol (4-[4-hydroxyphenyl]-2butanol), a competitive inhibitor of tyrosinase [132,133].

  Hydroquinone, a depigmenting agent widely used for the treatment of melasma, induces a reversible hypopigmentation of the skin at the site of application. In contrast, monobenzone, which is used as a depigmenting agent in the treatment of widespread vitiligo, can induce a permanent and generalized depigmentation.

- **Drug-induced leukoderma** – Potent topical or intralesional corticosteroids may induce hypopigmentation at the site of application, particularly in individuals with darkly pigmented skin. Depigmentation mimicking vitiligo may occur in patients treated with the epidermal growth factor receptor inhibitor gefitinib, the tyrosine kinase inhibitor imatinib

mesylate [134,135], interferon pegylated [136,137], and transdermal methylphenidate patch [131].

- **Hypopigmented mycosis fungoides** – Hypopigmented mycosis fungoides is an uncommon variant of early-stage mycosis fungoides seen more often in children and in patients with darkly pigmented skin (picture 16A-B) [138,139]. It presents with widespread hypopigmented patches with mild scaling and atrophy. Telangiectasias may also be present in the lesions. Histopathology does not show a complete absence of melanocytes but rather a minimal number of melanocytes as well as the morphologic and immunophenotypic findings suggestive of cutaneous T cell lymphoma. (See "Clinical manifestations, pathologic features, and diagnosis of mycosis fungoides".)

Additional conditions that should be differentiated from vitiligo include postinflammatory hypopigmentation, leukoderma associated with melanoma and scleroderma, and the late stages of treponematosis and onchocerciasis.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Vitiligo".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Vitiligo (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Epidemiology and pathogenesis** – Vitiligo is an acquired disorder of pigmentation, affecting approximately 1 percent of the world population. The pathogenesis of vitiligo is likely multifactorial and may involve genetic, autoimmune, neural, and biochemical factors and oxidative stress. (See 'Epidemiology' above and 'Pathogenesis' above.)

- **Clinical presentation** – Vitiligo typically presents with asymptomatic, depigmented macules and patches that lack clinical signs of inflammation (picture 1). Lesions can appear at any age and anywhere on the body. Based upon the distribution pattern of depigmented lesions, vitiligo is classified into two broad categories, segmental (picture 7) and nonsegmental (most common), and in several subtypes, such as generalized, acral or acrofacial, and universal (table 1). (See 'General features' above and 'Clinical classification' above.)

- **Associated disorders** – Vitiligo is frequently associated with autoimmune thyroid disease. Alopecia areata, psoriasis, inflammatory bowel disease, and several other autoimmune and genetic disorders have also been linked to vitiligo. (See 'Associated disorders' above.)

- **Diagnosis** – The diagnosis of vitiligo is made clinically in most cases. A skin biopsy can be performed in patients with hypopigmented or depigmented lesions of uncertain etiology. Given the relatively high frequency with which autoimmune thyroid disease occurs in patients with vitiligo, it is reasonable to screen all patients with vitiligo for thyroid function. (See 'Diagnosis' above and 'Laboratory studies' above.)

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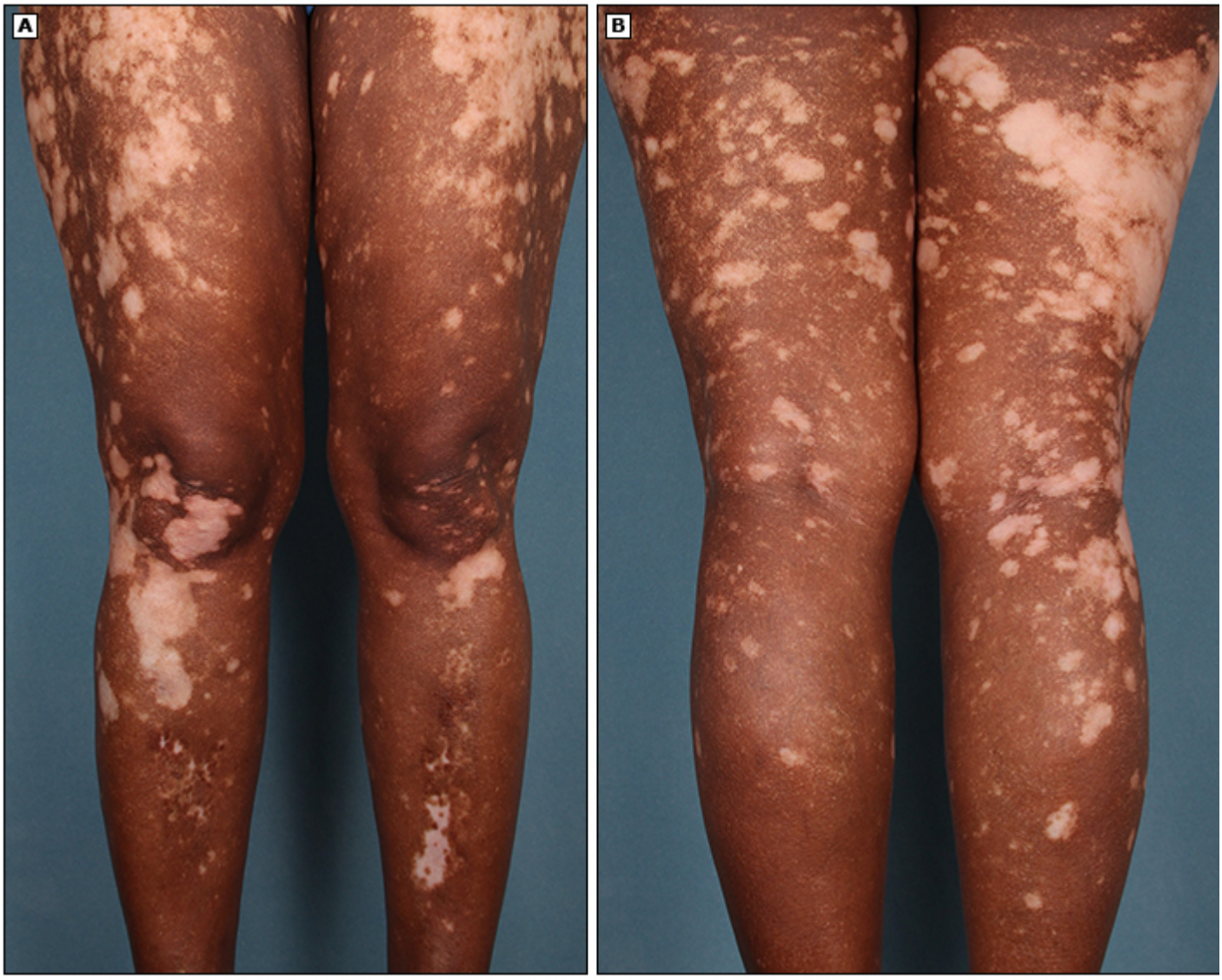
Topic 105109 Version 8.0

GRAPHICS

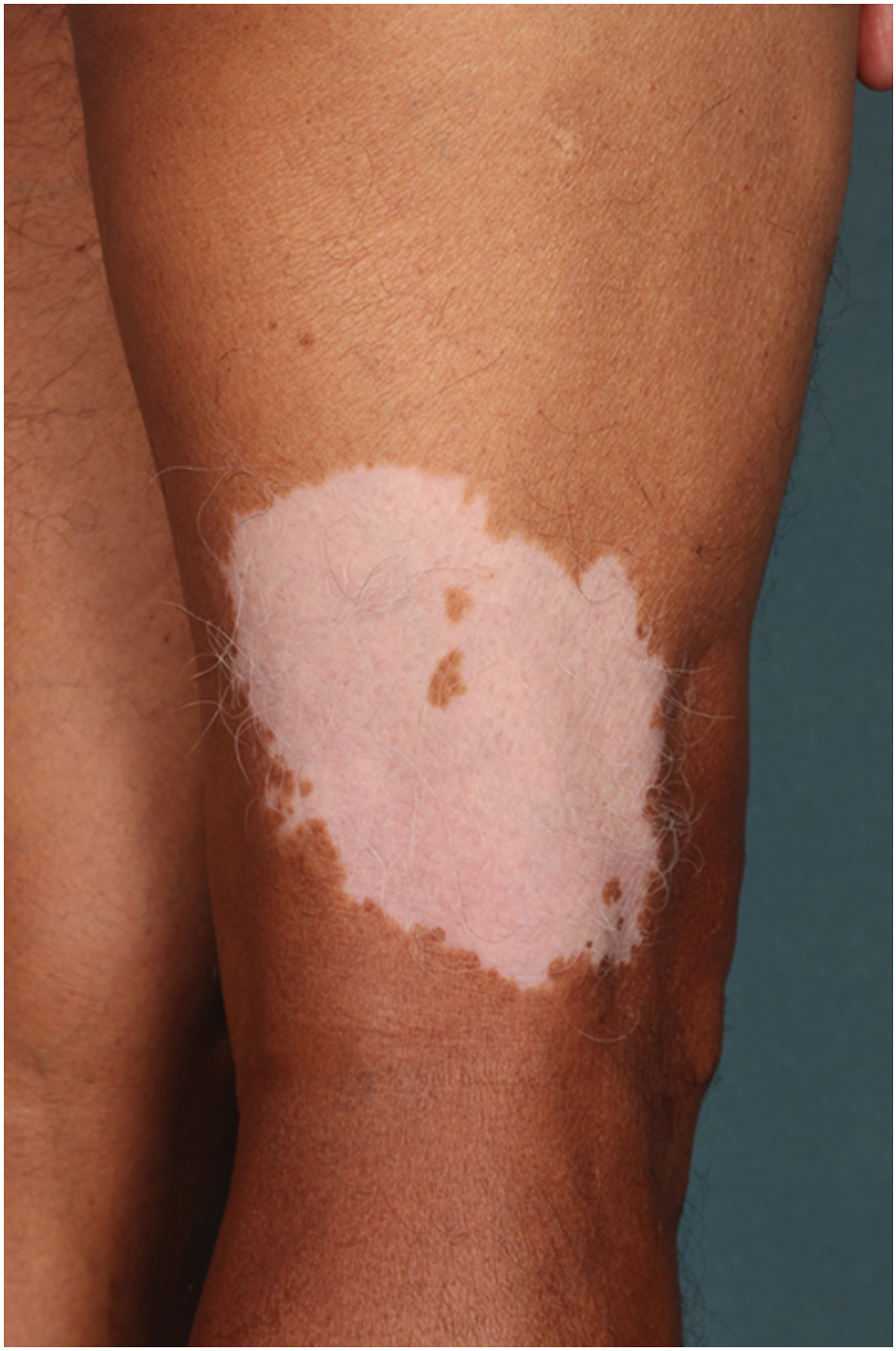
Vitiligo



Numerous white macules on the legs of this patient with generalized vitiligo.

Graphic 106463 Version 3.0

Vitiligo

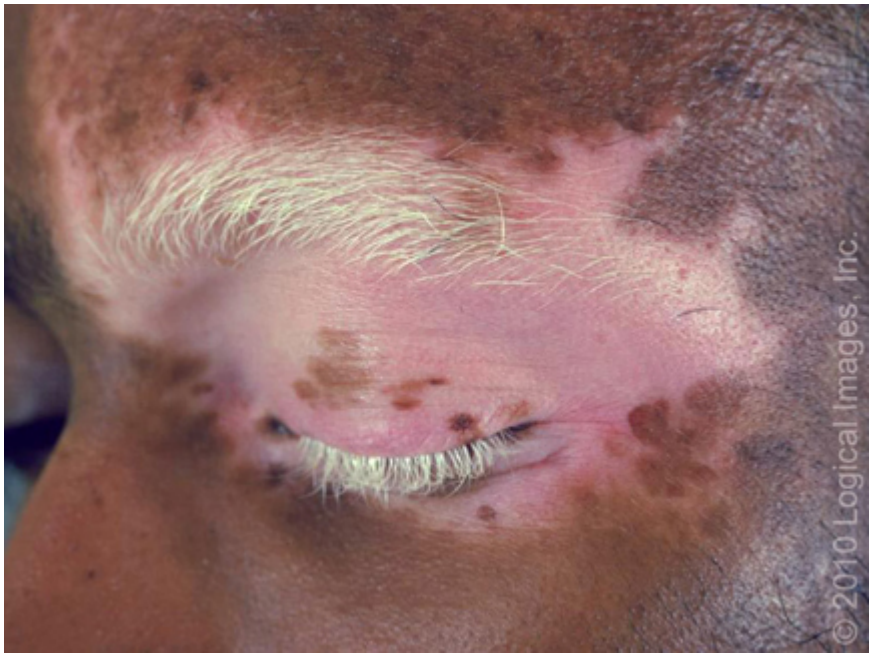


A large vitiligo patch is present on the leg of this patient. Note the depigmented hairs in the lesional skin.

Courtesy of Pearl E Grimes, MD.

Graphic 106464 Version 1.0

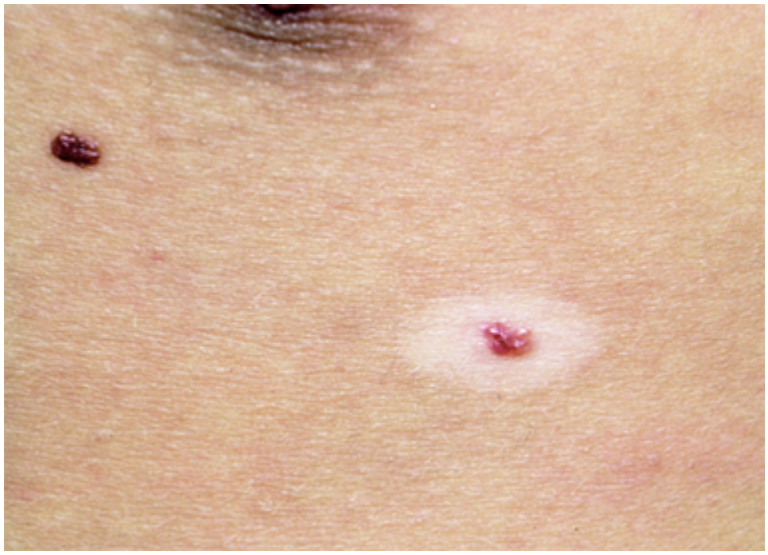
Vitiligo



A depigmented patch of vitiligo is present on the periocular skin. Note associated loss of pigment in the eyebrow and eyelashes.

Graphic 53173 Version 4.0

Halo nevus



An inflamed compound nevus is encircled by a white halo of depigmentation.

Graphic 57744 Version 2.0

Classification of vitiligo

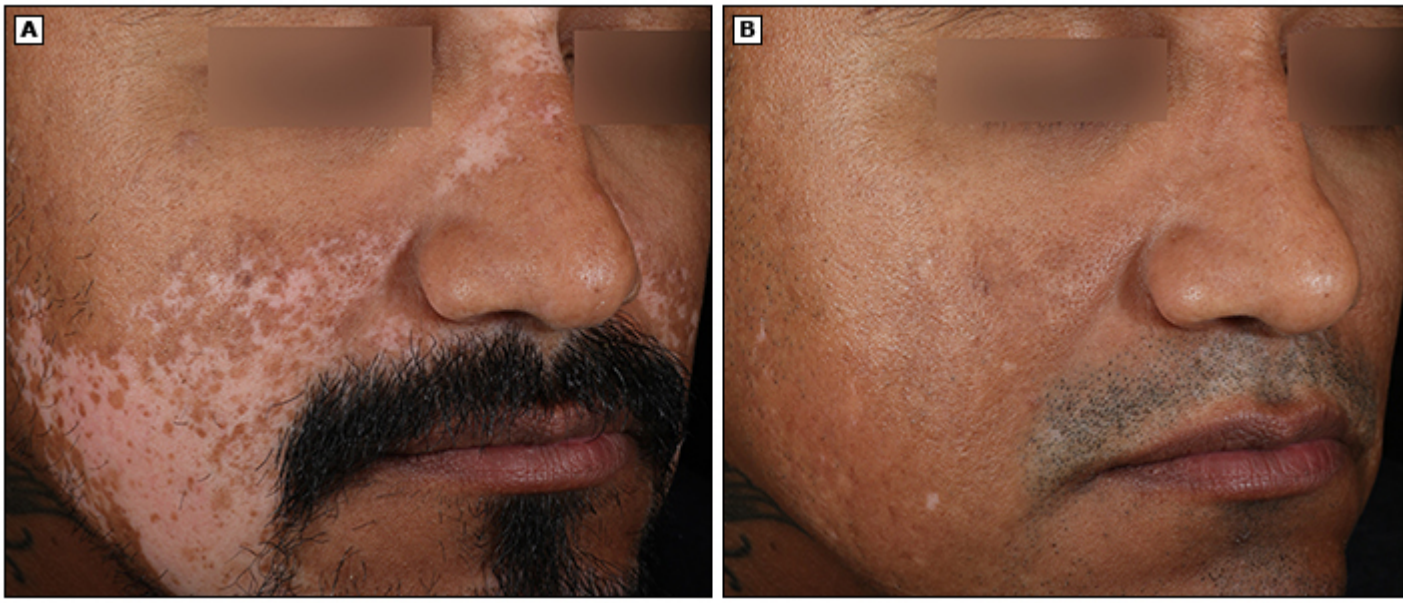
Type of vitiligo	Subtypes	Clinical features
Nonsegmental vitiligo	Generalized	▪ Symmetric, bilateral, depigmented macules in a random distribution over the entire body surface ▪ Onset usually before age 30 years ▪ Evolving over time
	Acral or acrofacial	▪ Only extremities and/or face involved
	Focal	
	Mucosal	▪ Multiple mucosal sites involved ▪ Usually associated with generalized vitiligo
	Universal	▪ Usually involves 80 to 90% of the body surface area
Segmental vitiligo	Monosegmental Bisegmental Plurisegmental	▪ Unilateral, asymmetric distribution of white macules that match a cutaneous segment (dermatomal distribution) ▪ Monosegmental most common ▪ Early age of onset ▪ Rapid stabilization
Mixed	Combination of nonsegmental and segmental vitiligo	
Rare variants	Vitiligo minor	▪ Incomplete depigmentation ▪ More common in dark-skinned individuals
	Follicular vitiligo	
Unclassified	Multifocal asymmetrical Single mucosal site involved	

Data from:

1. *Kovacevic M, Stanimirovic A, Vucic M, et al. Mixed vitiligo of Blaschko lines: a newly discovered presentation of vitiligo responsive to combination treatment. Dermatol Ther 2016 [Epub ahead of print].*
2. *Ezzedine K, Lim HW, Suzuki T, et al. Revised classification/nomenclature of vitiligo and related issues: The Vitiligo Global Issues Consensus Conference. Pigment Cell Melanoma Res 2012; 25:E1.*

Graphic 107278 Version 1.0

Vitiligo



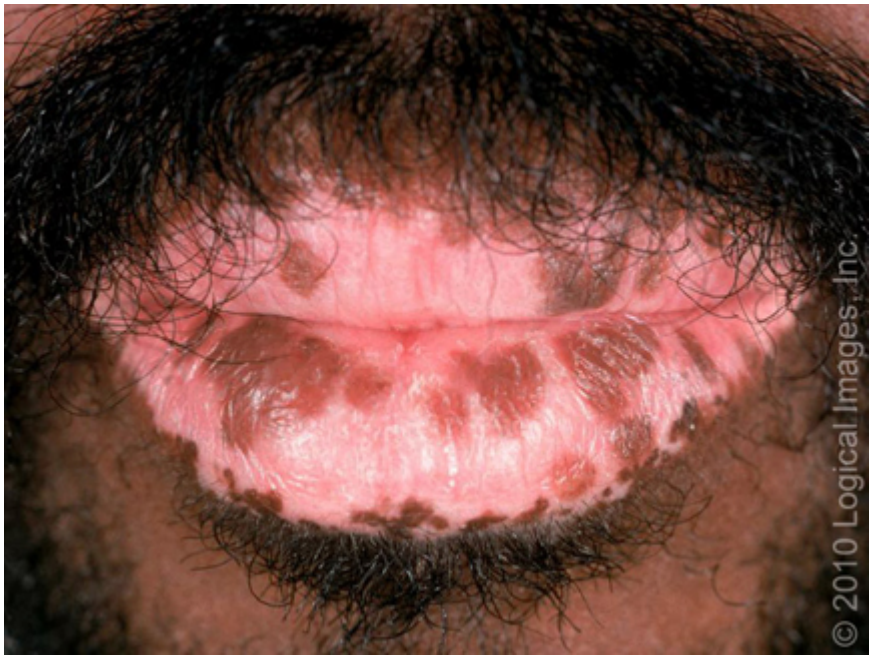
(A) Nonsegmental facial vitiligo before treatment.

(B) Complete repigmentation after treatment with topical tacrolimus for three months.

Courtesy of Pearl E Grimes, MD.

Graphic 105860 Version 1.0

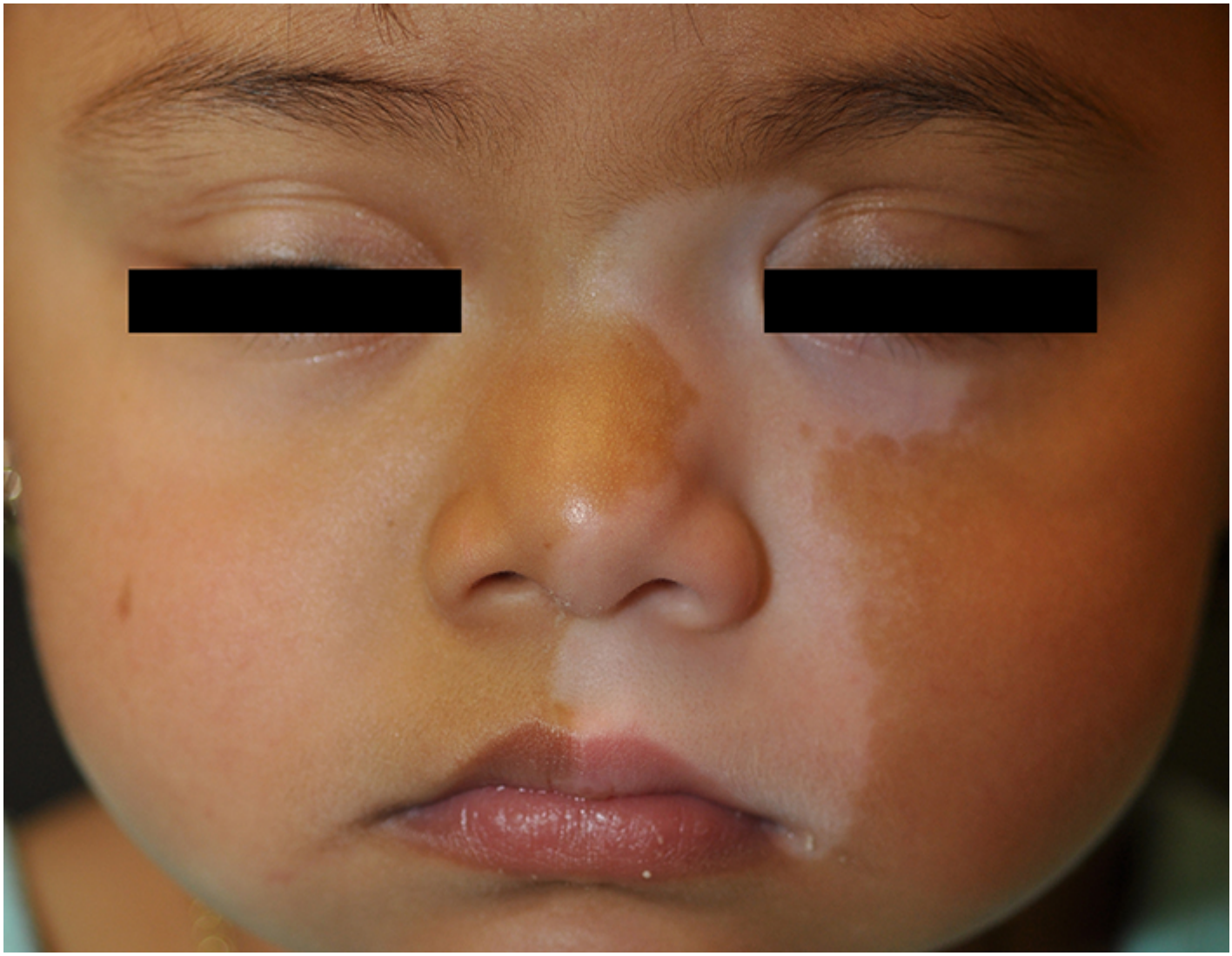
Vitiligo



Depigmented patches are present on the lips of this patient with vitiligo.

Graphic 51865 Version 4.0

Segmental vitiligo

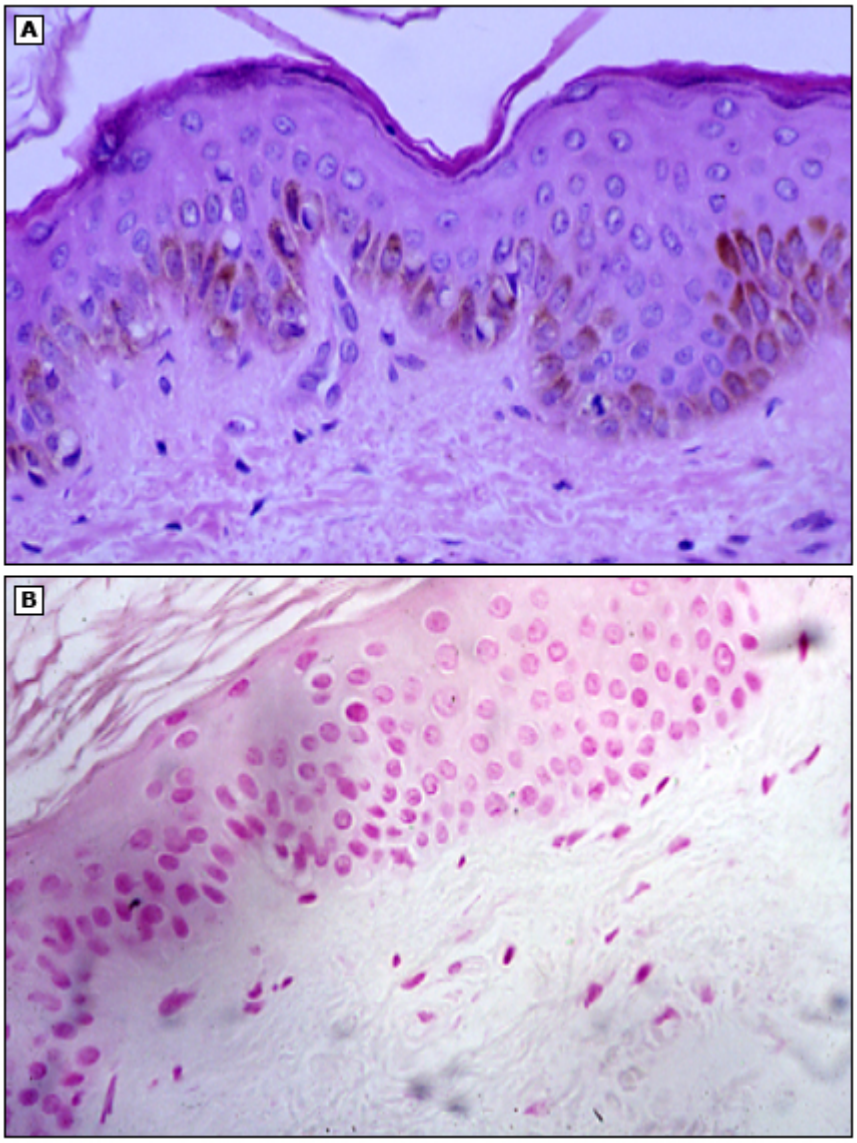


Segmental vitiligo in a child. Note the typical involvement of only one side of the face.

Courtesy of Pearl E Grimes, MD.

Graphic 105859 Version 3.0

Histopathologic features of vitiligo

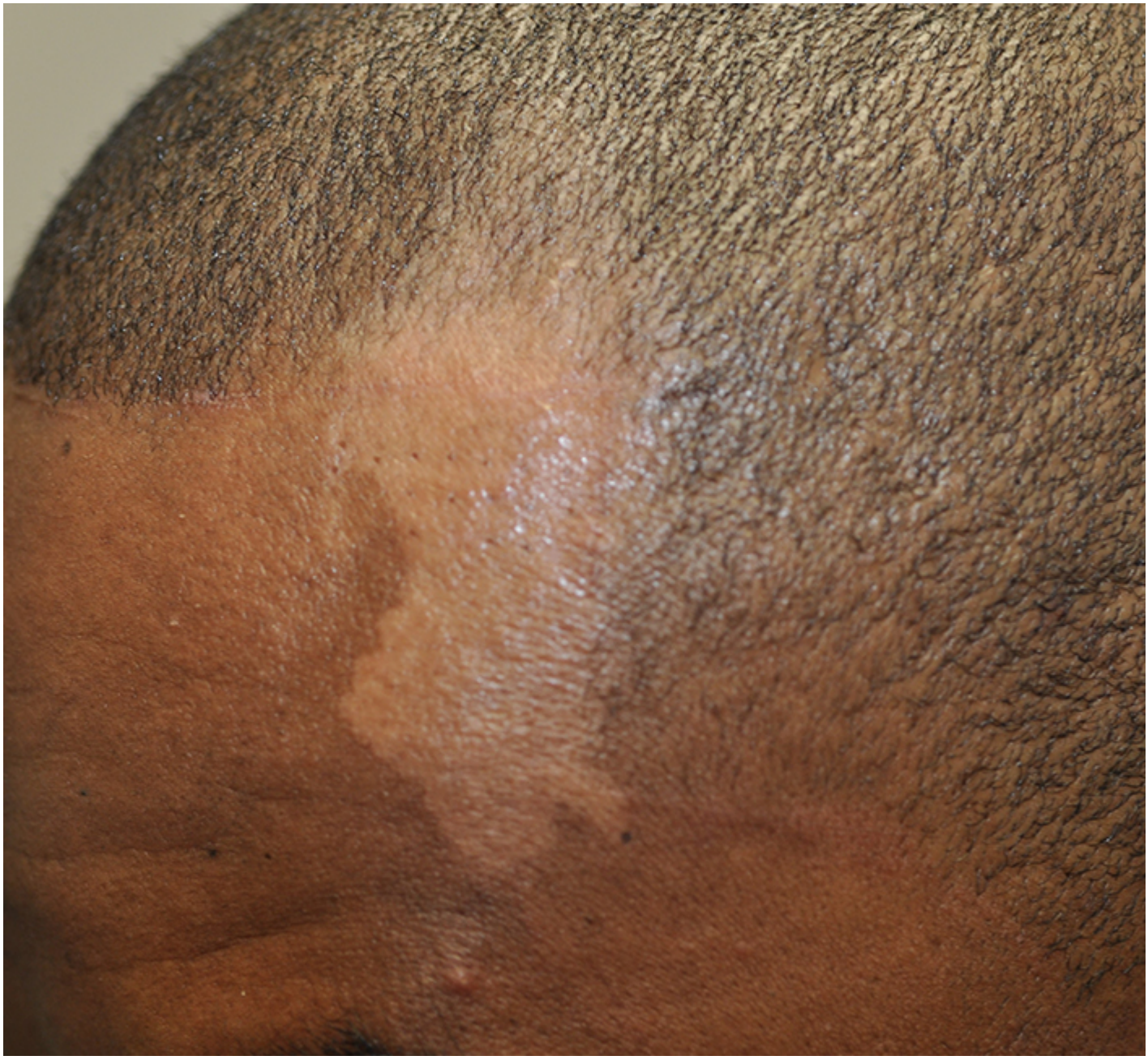


(A) Nonlesional skin and (B) lesional skin showing an absence of melanin and melanocytes. Hematoxylin and eosin stain.

Courtesy of Pearl E Grimes, MD.

Graphic 106596 Version 3.0

Nevus depigmentosus

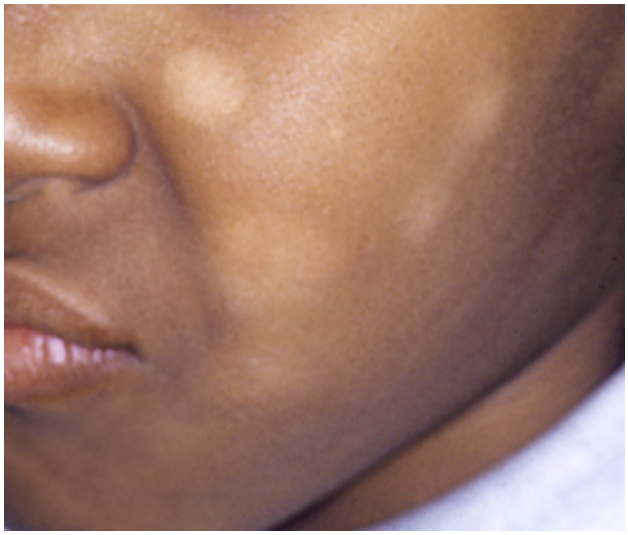


Nevus depigmentosus presenting as a hypopigmented, quasi-dermatomal lesion of the left forehead.

Courtesy of Pearl E Grimes, MD.

Graphic 106603 Version 2.0

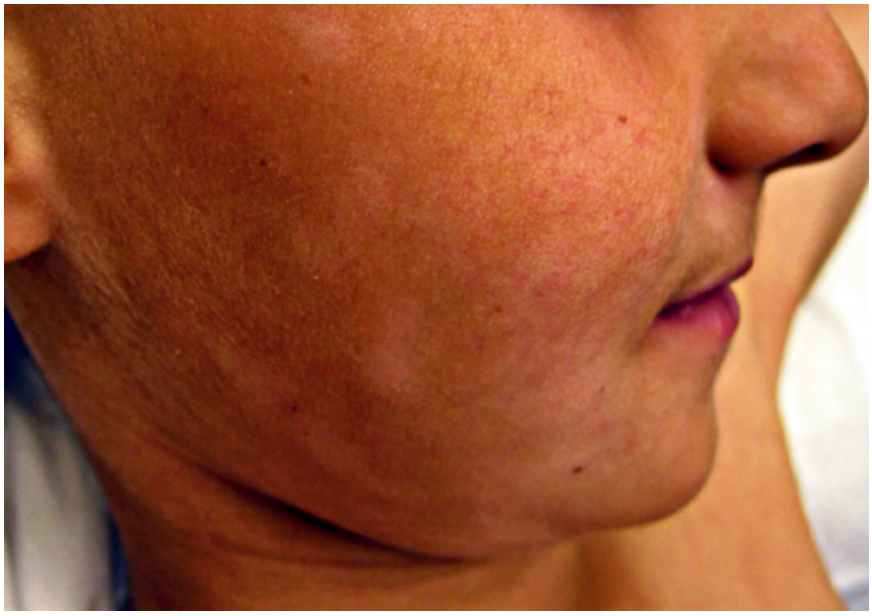
Pityriasis alba



Hypopigmented macules are present on the face of this young patient with pityriasis alba.

Graphic 60866 Version 8.0

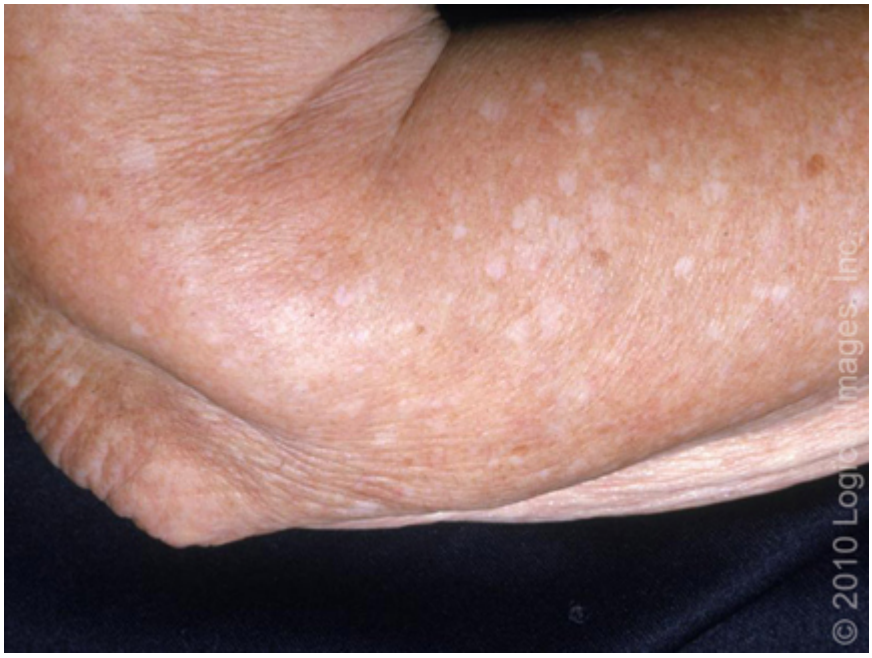
Pityriasis alba



Pityriasis alba. Hypopigmented, slightly scaly macules are present on this child's cheeks.

Graphic 73576 Version 2.0

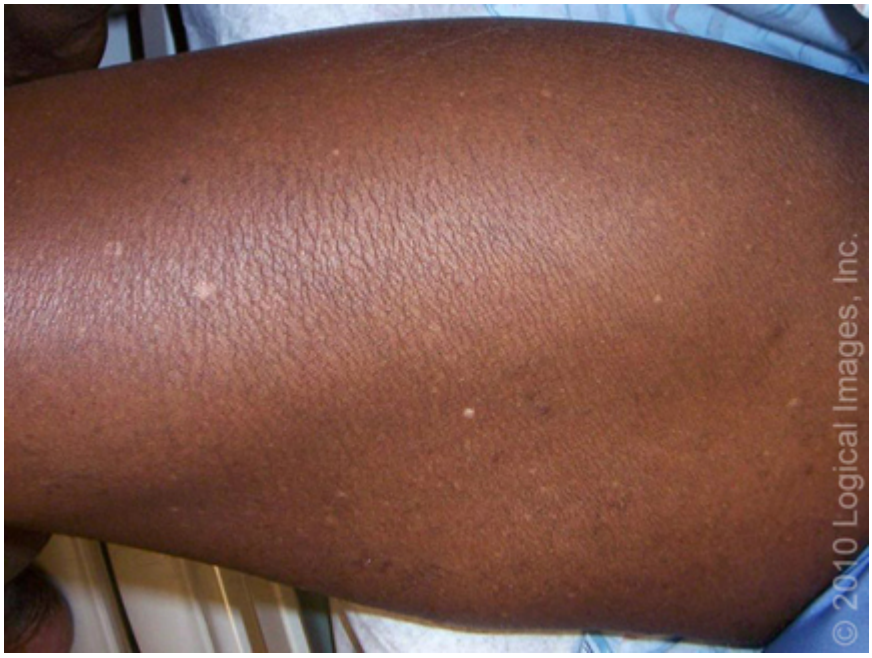
Idiopathic guttate hypomelanosis



Multiple small, hypopigmented macules on a background of sun-induced skin damage are present on the arm.

Graphic 67346 Version 5.0

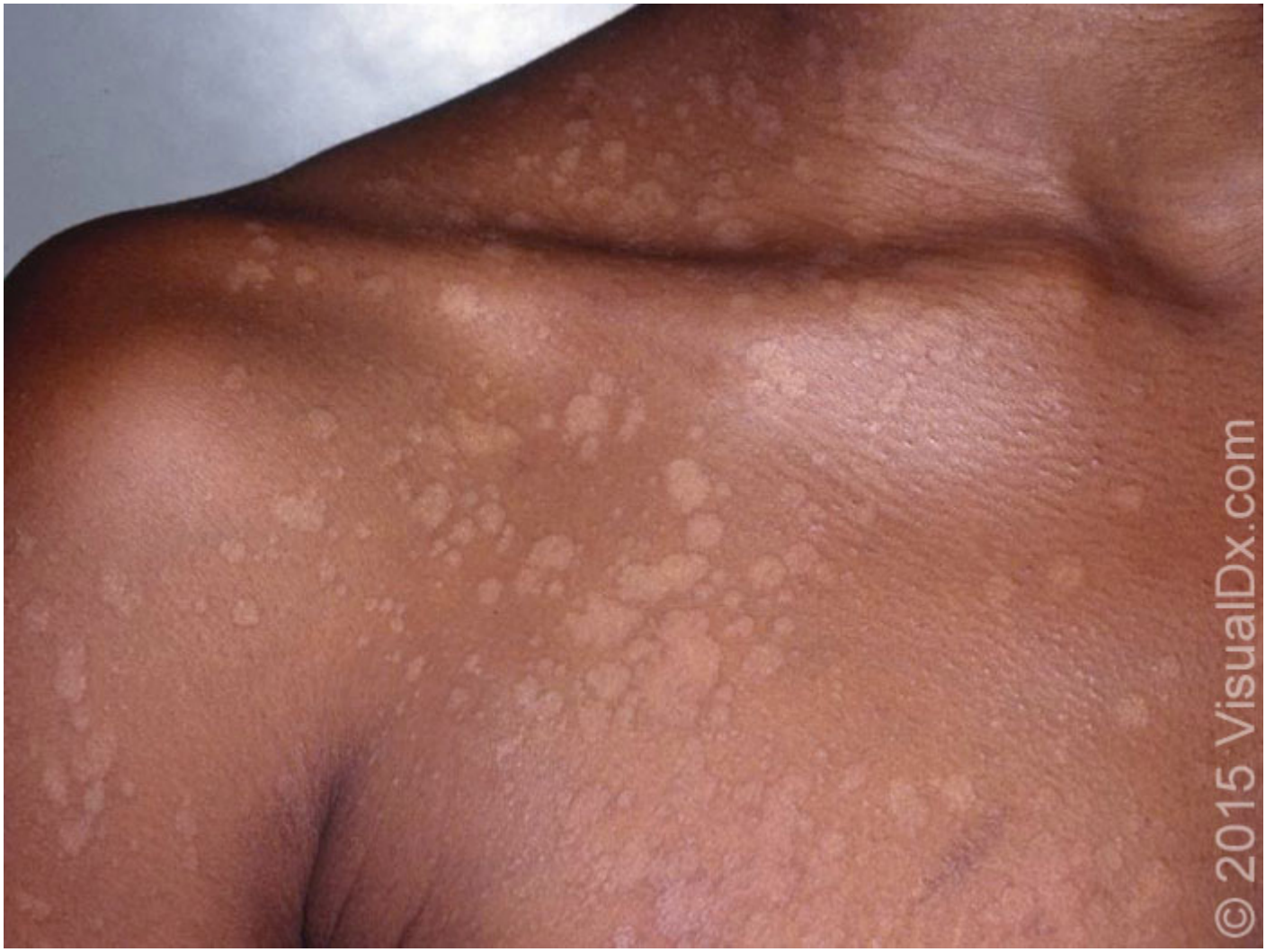
Idiopathic guttate hypomelanosis



Multiple small, hypopigmented macules are present on the thigh.

Graphic 61761 Version 4.0

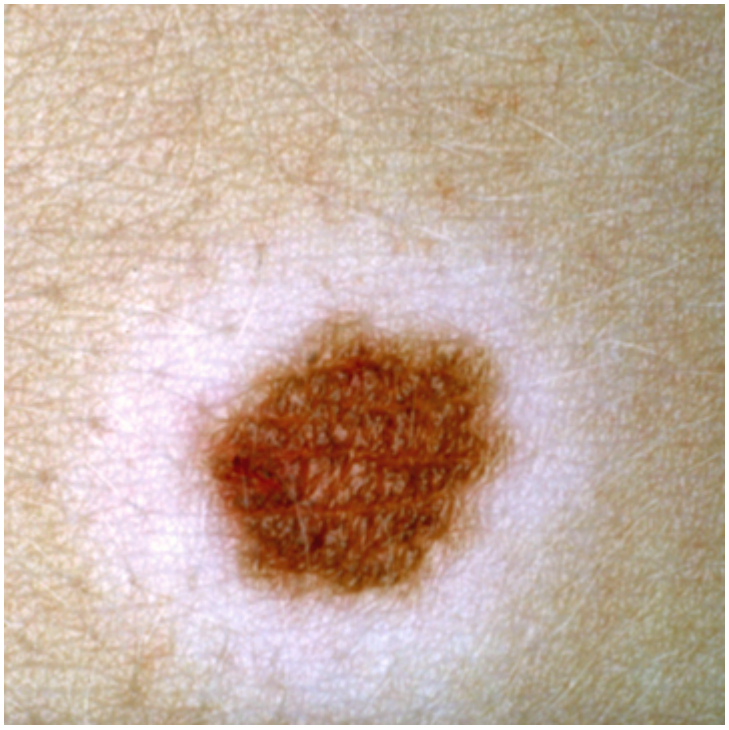
Tinea versicolor



Multiple hypopigmented macules on the neck, shoulder, and chest.

Graphic 100021 Version 2.0

Halo nevus (Sutton's nevus)

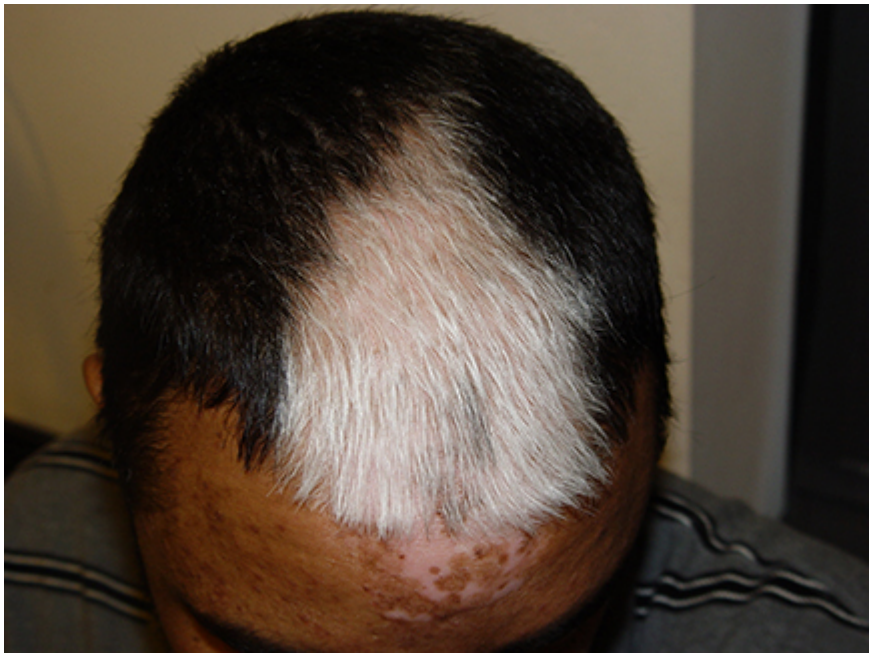


Stage I halo nevus with a characteristic depigmented rim.

Courtesy of Jean L Bolognia, MD, and Julie V Schaffer, MD.

Graphic 65988 Version 1.0

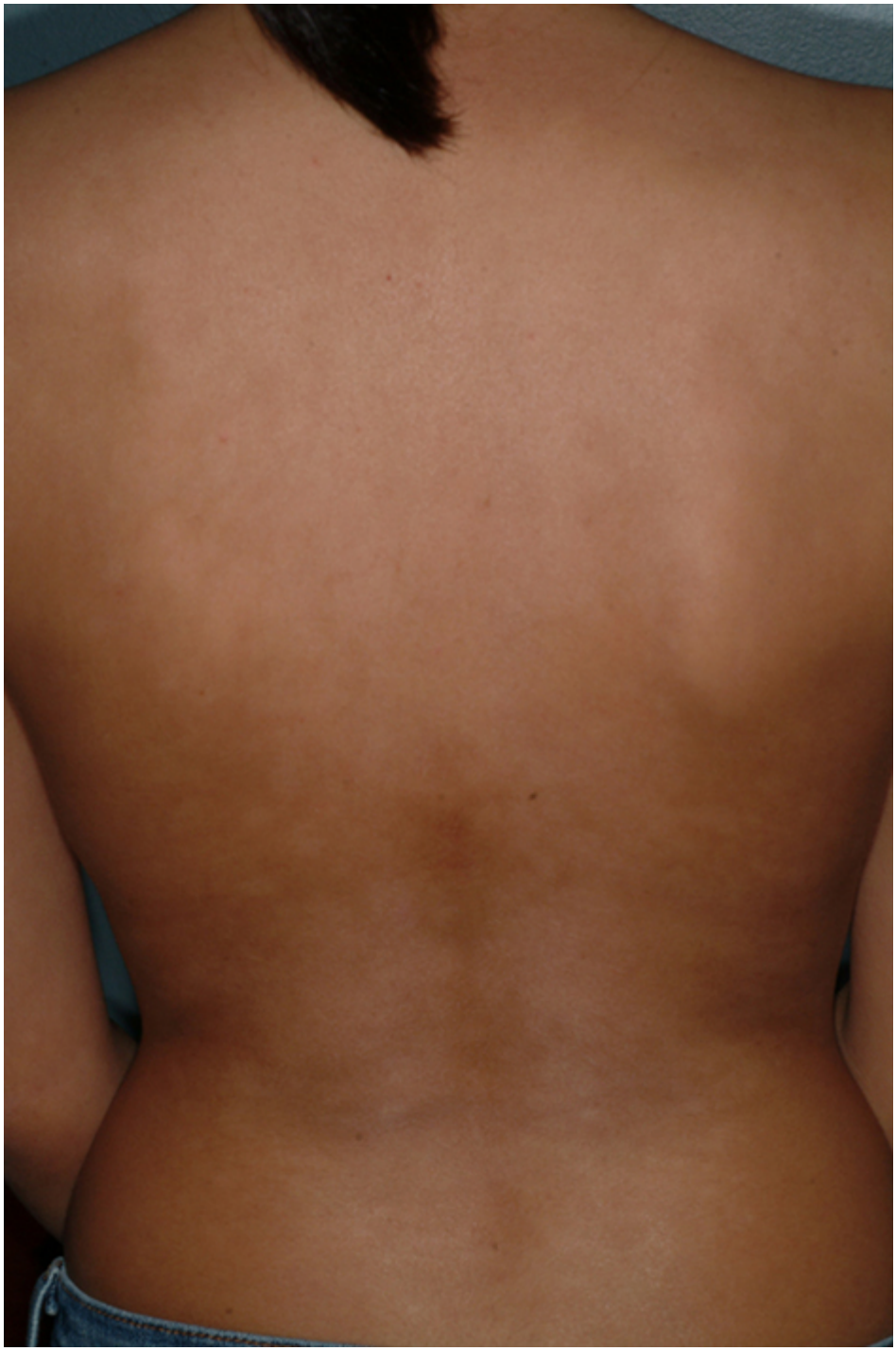
Piebaldism



A congenital depigmented patch with white hair is present on the scalp and forehead of this man with piebaldism. The patient also had depigmented patches on the trunk and extremities. Multiple family members had similar lesions.

Graphic 52591 Version 7.0

Progressive macular hypomelanosis of the back

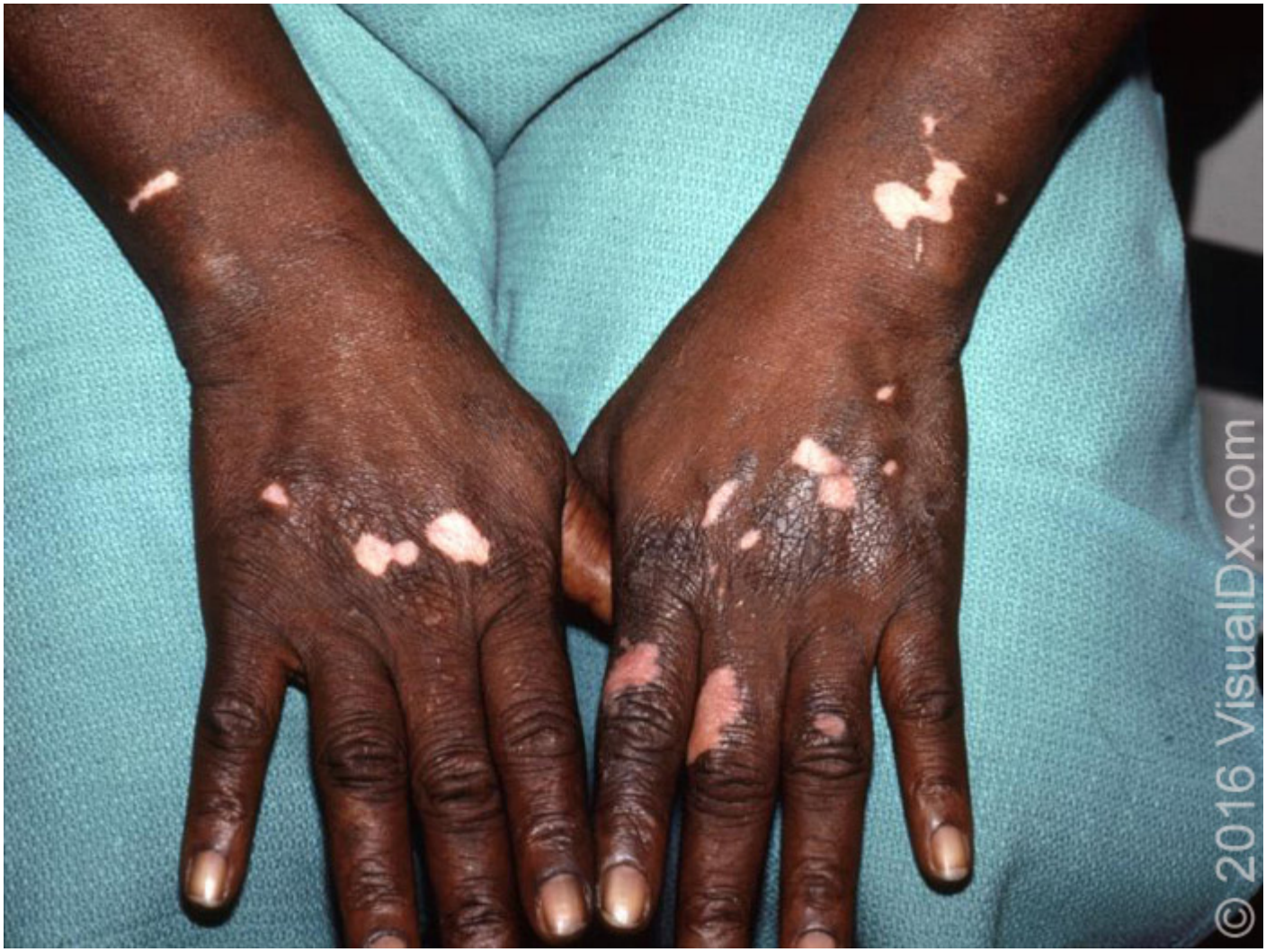


Progressive macular hypomelanosis showing hypopigmented areas of the back.

Courtesy of Pearl E Grimes, MD.

Graphic 107626 Version 2.0

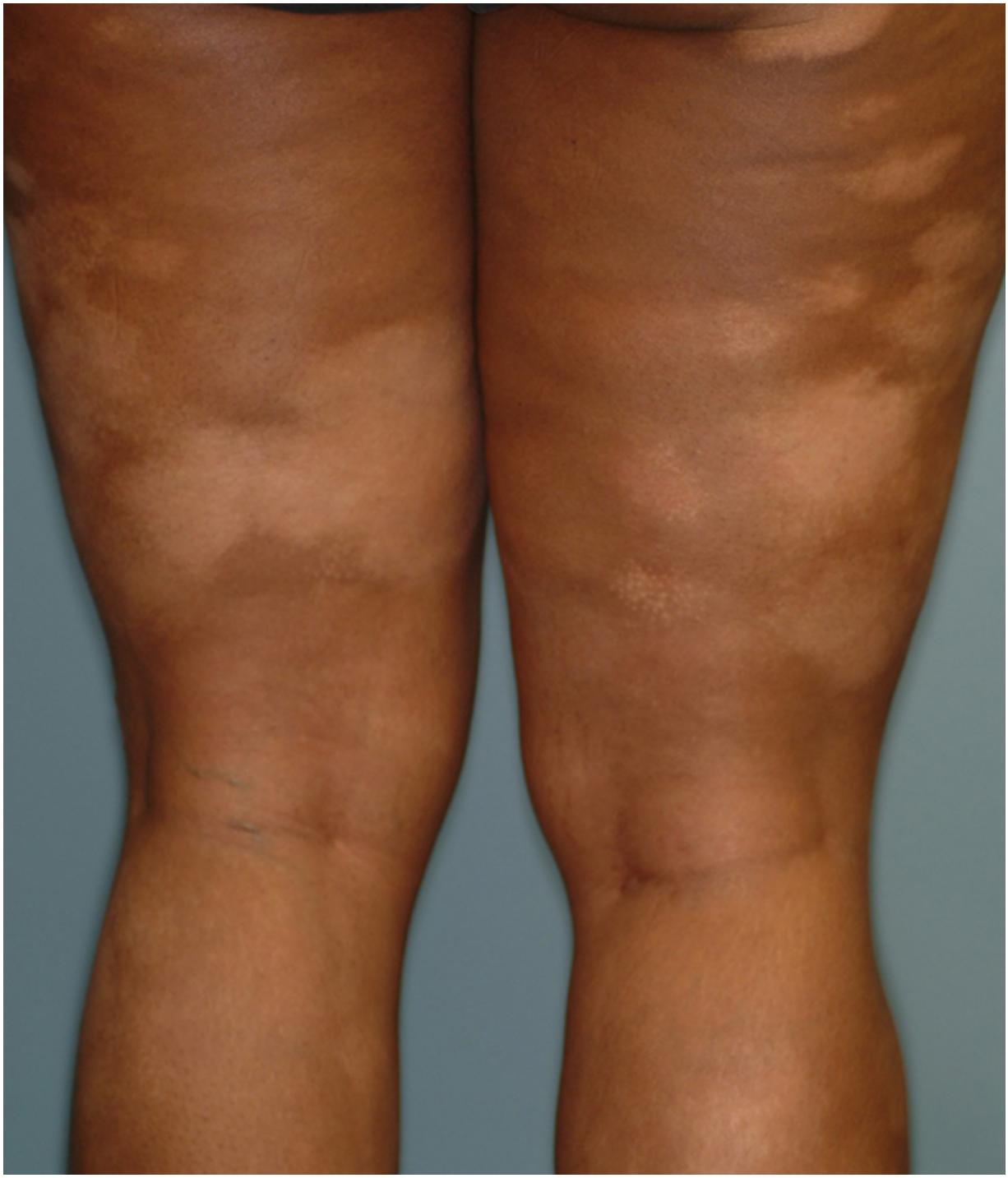
Chemical leukoderma



White macules mimicking vitiligo on the hands of a patient with chemical leukoderma.

Graphic 107622 Version 2.0

Hypopigmented mycosis fungoides

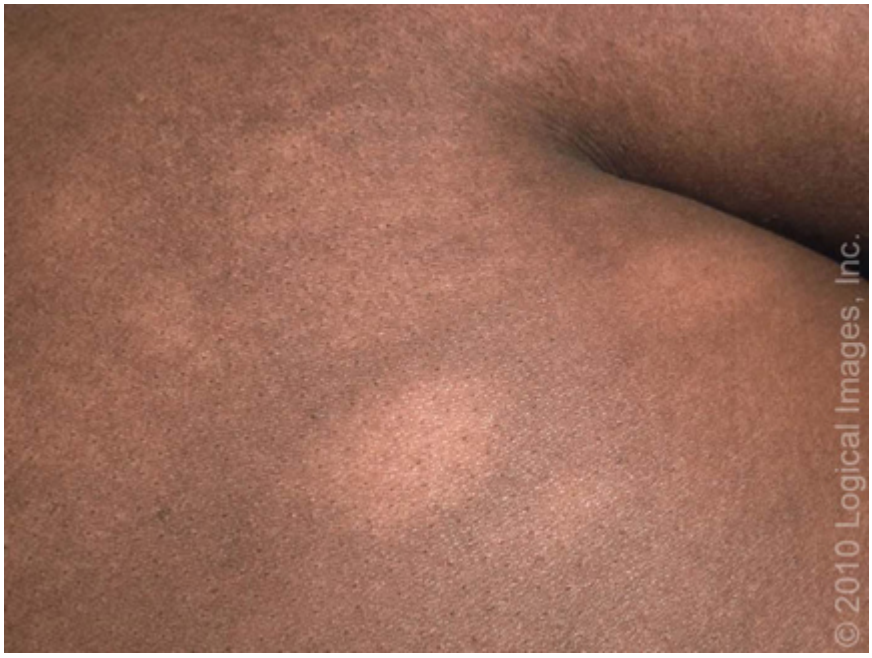


Hypopigmented and scaly patches are present on the legs of this patient. Biopsy showed cutaneous T cell lymphoma.

Courtesy of Pearl E Grimes, MD.

Graphic 106609 Version 2.0

Hypopigmented mycosis fungoides



Hypopigmented patches are present in this patient with mycosis fungoides.

Graphic 71926 Version 7.0

Contributor Disclosures

Pearl E Grimes, MD Grant/Research/Clinical Trial Support: Acrutis [Vitiligo];Clinuvel Pharmaceuticals [Pigmentation, vitiligo];Incyte [Hypopigmentation, vitiligo];LaserOptek [Hypopigmentation];Pfizer [Hypopigmentation, vitiligo];Sun Pharmaceuticals [Vitiligo];VT Technologies [Pigmentation]. Consultant/Advisory Boards: Clarify Medical [Vitiligo];Dermaforce [Hyperpigmentation];Incyte [Vitiligo];L'Oréal [Hyperpigmentation];Procter & Gamble [Hyperpigmentation, cosmetics]. All of the relevant financial relationships listed have been mitigated. **Hensin Tsao, MD, PhD** Consultant/Advisory Boards: Epiphany Dermatology [Basal cell carcinoma, melanoma, nevi, skin cancer screening]; Lazarus AI [Melanoma]. All of the relevant financial relationships listed have been mitigated. **Andrew F Alexis, MD, MPH** Grant/Research/Clinical Trial Support: Almirall [Melasma];Amgen [Central centrifugal cicatricial alopecia];Arcutis Biotherapeutics [Seborrheic dermatitis, atopic dermatitis];Bausch Health Companies [Acne, psoriasis];Bristol Myers Squibb [Melasma];Cara Therapeutics [Atopic dermatitis];Galderma [Melasma];LEO Pharma [Melasma];Menlo Therapeutics [Melasma];Novartis [Melasma]. Consultant/Advisory Boards: AbbVie [Atopic dermatitis];Allergan [Melasma, aesthetic dermatology];Almirall [Acne];Amgen [Psoriasis];Arcutis Biotherapeutics [Seborrheic dermatitis];Bausch Health Companies [Acne, psoriasis];Beiersdorf [Atopic dermatitis, photoprotection];Bristol-Myers Squibb [Psoriasis];Dermavant Sciences [Atopic dermatitis, psoriasis];Galderma [Melasma];Janssen Pharmaceuticals [Atopic dermatitis];LEO Pharma [Melasma];L'Oréal [Acne, photoprotection, melasma];Menlo Therapeutics [Melasma, prurigo nodularis];Pfizer [Atopic dermatitis];Sanofi-Regeneron Pharmaceuticals [Atopic dermatitis];Sol-Gel [Acne];UCB [Psoriasis];VYNE Therapeutics [Acne]. Speaker's Bureau: AstraZeneca [Atopic dermatitis];Pfizer [Atopic dermatitis];Regeneron Pharmaceuticals [Atopic dermatitis];Sanofi Genzyme [Atopic dermatitis]. All of the relevant financial relationships listed have been mitigated. **Rosamaria Corona, MD, DSc** No relevant financial relationship(s) with ineligible companies to disclose.

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