

New discoveries in the pathogenesis and classification of vitiligo



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Learning objectives

After completing this learning activity, participants should be able to categorize the different forms and presentations of vitiligo; recognize the key features that distinguish active vitiligo; and discuss the mechanisms that influence the initiation and progression of vitiligo.

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).

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Vitiligo is a common autoimmune disease that progressively destroys melanocytes in the skin, resulting in the appearance of patchy depigmentation. This disfiguring condition frequently affects the face and other visible areas of the body, which can be psychologically devastating. The onset of vitiligo often occurs in younger individuals and progresses for life, resulting in a heavy burden of disease and decreased quality of life. Presentation patterns of vitiligo vary, and recognition of these patterns provides both diagnostic and prognostic clues. Recent insights into disease pathogenesis offer a better understanding of the natural history of the disease, its associations, and potential for future treatments. The first article in this continuing medical education series outlines typical and atypical presentations of vitiligo, how they reflect disease activity, prognosis, and response to treatment. Finally, we discuss disease associations, risk factors, and our current understanding of disease pathogenesis. (J Am Acad Dermatol 2017;77:1-13.)

Key words: chemical leukoderma; confetti depigmentation; halo nevi; leukoderma; segmental vitiligo; vitiligo; vitiligo pathogenesis.

Vitiligo patients are often told that their vitiligo “isn’t a big deal,” that there is “nothing that can be done for it,” and that they “should just

learn to live with it” by their physicians. This is a disservice, because patients often arrive in a dermatologist’s clinic discouraged after years of disease

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progression. Those with long-standing disease (>1-2 years) treated with narrowband ultraviolet B light therapy (NB-UVB) demonstrate lower efficacy compared to patients with recent onset vitiligo.¹⁻³ Therefore, recognizing vitiligo as a treatable disease and initiating appropriate treatment early is a critical step in helping these patients both physically and psychologically. Despite this, many patients with even long-standing disease can respond to treatment, and so while patients should be encouraged to initiate treatment early in their disease, no one should be discouraged from attempting treatment. New discoveries in the past 5 years have improved our understanding of the disease. The purpose of this review is to empower dermatologists to approach the diagnosis, classification, and management of vitiligo patients in a way that will lead to improved outcomes.

EPIDEMIOLOGY AND QUALITY OF LIFE

Key points

- **Vitiligo is common, affecting 0.5% to 2% of the world's population without preference for race or sex**
- **The psychological impact on quality of life is similar to those with psoriasis and atopic dermatitis**

Unlike diseases that require medical treatment for survival, such as juvenile diabetes or thyroiditis, determining the true incidence of vitiligo is challenging, because patients with vitiligo may not seek medical care. A few prospective survey studies, retrospective observational studies, and prospective studies in selected populations, such as those attending dermatology clinics, are available, but these may underestimate or overestimate the incidence, depending on the approach. Based on these studies, vitiligo reportedly affects 0.5% to 2% of the world's population, without clear preference for race or sex, although women may be more likely to present for treatment and respond to surveys.⁴⁻⁷ Almost 50% of patients present before 20 years of age,⁸ and many of these present before 10 years of age.⁹

Vitiligo is not "just a cosmetic condition"—it is a psychologically devastating autoimmune disease.¹⁰⁻¹³ Studies have shown that the effect vitiligo has on quality of life, particularly psychological impairment, is similar to other skin diseases, such as psoriasis and atopic dermatitis.¹⁴ The Dermatology Life Quality Index (DLQI) is a simple 10-item questionnaire that aims to measure how much skin diseases impact a patients' life, and scores vary from 0 (no impact) to 30 (highest impact). Differences in DLQI scores are noted in different cultural groups, reflecting the increased



Fig 1. Vitiligo koebnerizing within thyroidectomy scar.

stigma and social ramifications of having vitiligo in some communities. For example, DLQI scores were 4.95 in a Belgian study, but 7.06 in Indian patients with a successful treatment outcome and 13.12 in those who failed treatment.¹⁵ Clinicians should take their patients' concerns about vitiligo seriously, having a low threshold for referring patients to counseling services if mood disturbance or significant stress is detected.

PRESENTATIONS AND CLINICAL CLASSIFICATION

Key points

- **Patterns of vitiligo lesions predict progression and treatment responses**
- **The segmental variant of vitiligo is rapidly progressive but stabilizes quickly, and is less responsive to treatment**
- **Progressive disease is marked by inflammatory, trichrome, and confetti-like lesions, as well as the Koebner phenomenon**

Depigmentation of the skin and hair follicles is the clinical hallmark of vitiligo. This results in white, often symmetrical macules and patches, usually increasing in number and size over time, and frequently appearing in visible areas like the face and extremities. In fair-skinned patients, vitiligo is usually first noted in sun-exposed sites because of tanning of unaffected skin. Several factors have been associated with the onset of disease, including severe sunburn, pregnancy, cutaneous trauma,¹⁶ and significant psychological stress.¹⁷ Patients may exhibit the Koebner phenomenon, in which new lesions of vitiligo appear in areas of trauma (Fig 1).

Localized types of vitiligo include focal and mucosal vitiligo. Focal vitiligo refers to an isolated, small, depigmented patch (10-15 cm²) that lacks an obvious, unilateral segmental distribution and does not progress for at least 2 years.¹⁸ The term mucosal vitiligo is typically used when only 1 site in isolation is



Fig 2. Lip-tip variant of vitiligo in a young African girl.



Fig 3. Universal vitiligo in an Asian man.

noted in the oral or genital region. Acrofacial vitiligo is usually limited to the head, hands, and feet. Distal finger, toe, and facial orifice involvement is often named “lip-tip” vitiligo, commonly seen in South Asia, and is resistant to treatment^{19,20} (Fig 2). Universal vitiligo refers to complete or near-complete depigmentation of the skin, which may or may not include body hair ($\geq 80\%$ of BSA¹⁸; Fig 3).

Occupational, contact, or chemical leukoderma describes depigmentation that is induced by exposure to phenols or similar chemicals. While



Fig 4. Segmental variant of vitiligo on the abdomen of an adolescent boy.

depigmentation initially starts at sites of exposure, the development of remote lesions with progression to a more widespread, typical pattern is common.²¹ This disease is indistinguishable from classical vitiligo by clinical examination or histology,²² and therefore chemical leukoderma does not appear to be distinct from vitiligo, but may be better classified as chemically induced vitiligo.²³

In segmental vitiligo, the progressive loss of melanocytes results in a unilateral patch of depigmentation that may be arranged in a linear or block-like pattern (Figs 4 and 5).²⁴ It has been frequently mischaracterized as “dermatomal vitiligo” despite the fact that patterns of depigmentation rarely follow a dermatome. Segmental patterns of vitiligo correlate best with mosaic skin disorders, suggesting that it may be influenced by somatic mutations in developing melanocytes (see section on pathophysiology).²⁵ The term “dermatomal vitiligo” should therefore no longer be used.

Segmental vitiligo frequently affects the face and progresses quickly over 6 months to 2 years with rapid onset of leukotrichia, but typically stabilizes without treatment. It is 10 times less common than other variants of vitiligo, and early leukotrichia is a hallmark.²⁴ The majority (87%) of cases occur before 30 years of age, with some reports describing development as early as 6 weeks after birth.²⁶ This variant is less responsive to treatment than other variants, possibly because of its more frequent association with leukotrichia and the resulting lack of melanocyte reservoirs available for repigmentation.

In rare cases, patients may have a typical segmental pattern of vitiligo and then develop additional lesions outside of this region, a presentation labeled mixed vitiligo.²⁷ Patients with mixed vitiligo exhibit a poor response to ultraviolet light exposure in segmental lesions but a good response elsewhere. Those with halo nevi, leukotrichia, and an initial truncal lesion of segmental vitiligo are more likely to progress to mixed vitiligo



Fig 5. Segmental variant of vitiligo on the face and neck of young boy.

Table I. Classification of vitiligo

Type	Subtype
Vitiligo	Acrofacial, focal, mucosal (>1 mucosal site), generalized, universal, mixed (associated with segmental vitiligo), and rare variants
Segmental vitiligo/undetermined/unclassified	Unisegmental and multisegmental

over time.²⁸ A 2012 international consensus report¹⁸ recommended that the umbrella term “vitiligo” be used for all forms of vitiligo (Table I) except the segmental variant, which should have a special classification because of its distinct prognosis and response to treatment.²⁹

Halo nevi

Halo nevi (also called Sutton nevi) are characterized by depigmentation surrounding a nevus, forming a halo. While they are common in healthy individuals, they are 8 to 10 times more common in patients with vitiligo.³⁰ The presence of multiple halo nevi is a marker of cellular autoimmunity against nested melanocytes and may indicate an increased risk of vitiligo in affected individuals, particularly those with a family history of the disease. Individuals with vitiligo who also have congenital or halo nevi reportedly have fewer acral lesions of vitiligo and more central involvement.^{25,31}

Vitiligo in patients with melanoma

Epidermal depigmentation may also be seen in patients with malignant melanoma. It is a good prognostic sign when occurring either spontaneously or when induced by newer melanoma treatments.³²⁻³⁴ While this phenomenon has been



Fig 6. Trichrome pattern on the neck and shoulders.

given descriptive names in the past to differentiate it from vitiligo, the clinical appearance of depigmentation and its histopathology are indistinguishable from vitiligo.^{35,36} In addition, similar to vitiligo, the depigmentation in melanoma patients is mediated by autoreactive CD8⁺ T cells that attack and kill melanocytes by recognizing melanocyte-specific antigens that directly overlap with vitiligo³⁷ (see section on vitiligo pathogenesis). Therefore, this process should be characterized as new onset vitiligo in patients with melanoma rather than a distinct entity.

Clinical markers of disease activity

The most extensively characterized clinical markers of active, progressive disease include the Koebner phenomenon, trichrome lesions, inflammatory lesions, and confetti-like depigmentation. A recent study described greater BSA and a poorer response to treatment when any type of Koebner phenomenon is present.³⁸ Trichrome lesions (Fig 6) have 3 colors in close proximity—depigmented lesional skin, normally pigmented skin, and a zone of hypopigmented skin, usually at the border. This presentation has been associated with active, rapidly progressing disease.³⁹ Inflammatory vitiligo (Fig 7) is an uncommon presentation characterized by erythema, scale, and pruritus within hypopigmented or depigmented lesions, particularly at the lesional border. Early histologic studies showed that this presentation has a significant interface dermatitis comprised of T cells.⁴⁰ The inflammatory phase may be short-lived, but causes rapid depigmentation. Confetti-like depigmentation has been recently described as a marker of rapidly progressive vitiligo, with patients exhibiting a higher Vitiligo Disease Activity Score and Koebner Phenomenon Vitiligo Score, which correlate with more active, progressive, and aggressive disease.⁴¹ This clinical appearance is characterized by numerous depigmented macules



Fig 7. Inflammatory type of vitiligo with erythema and scale.

(1-5 mm in diameter) clustered in groups that are frequently seen at the border of larger existing lesions (Fig 8). These markers of severity are important when assessing the patient and developing a management plan.

DIAGNOSIS

Key points

- **Vitiligo is usually a clinical diagnosis**
- **Wood's lamp examination helps to confirm the diagnosis and extent of disease in fair-skinned individuals**
- **The primary differential diagnoses include diseases of hypopigmentation**

Vitiligo is usually a clinical diagnosis, often aided by a thorough history and examination (Table II). Wood's lamp examination of vitiligo reveals a chalky white enhancement of depigmented skin, while hypopigmented skin is not enhanced. Other, inherited causes of depigmentation are often noted at birth, remain stable over time, occur in the context of other developmental or systemic problems, and often demonstrate a positive family history. When diagnosing vitiligo, it is essential to exclude other conditions causing hypopigmentation and depigmentation (Tables III and IV). Rarely, histopathologic examination may be necessary to confirm the diagnosis.

The differential diagnosis of vitiligo includes hypopigmented dermatoses, such as progressive macular hypomelanosis, tinea versicolor, pityriasis alba, and hypopigmented mycosis fungoides. Nevus depigmentosus is the main differential diagnoses of segmental vitiligo and focal vitiligo (Table IV). Nevus depigmentosus is usually present at birth or appears within the first few months of life, grows in proportion to the child, and often appears after first sun exposure, which darkens the surrounding skin and reveals its presence. Unlike segmental vitiligo, the lesions of nevus depigmentosus do not expand over time, are usually hypopigmented rather than depigmented, are not associated with leukotrichia, and typically reveal a jagged border, while vitiligo



Fig 8. Confetti-like lesions on the dorsal aspect of the foot.

lesions have a smooth border. No alteration in texture, sensation, or hyperpigmented border is noted. Biopsy specimens reveal approximately normal numbers of melanocytes, but melanin production is decreased.⁴² Nevus depigmentosus is off-white under Wood's lamp while vitiligo is chalky white.

Histology

Lesional skin in vitiligo shows complete or near-complete loss of epidermal pigmentation (Fontana–Masson stain) with an absence of melanocytes at the basal layer.⁴³ Early lesions demonstrate a subtle interface dermatitis consisting of CD8⁺ cytotoxic T cells infiltrating the epidermis in close approximation to melanocytes. The expanding edges of active lesions may reveal a perivascular and perifollicular lymphocytic infiltrate. Electron microscopy of lesional borders reveals vacuolization of melanocytes and keratinocytes. Established lesions show sparse inflammation, likely because the T-cell infiltrate has cleared by the time the epidermis becomes visibly depigmented. In fact, visible depigmentation of the skin may not become apparent for up to 48 days after apoptosis of melanocytes has occurred.⁴⁴

DISEASE ASSOCIATIONS

Key points

- **Vitiligo may present with systemic changes, including inflammation of the eye and ear**
- **Autoimmune diseases are more prevalent in patients with vitiligo and their family members**

Table II. Approach to history and examination of a patient with vitiligo

History	Examination
Age of onset	Fitzpatrick skin phototype
Location of first lesion	Distribution (whole body with Wood's lamp/light)
Length of stability/rapidity of progression	Morphology
Areas of involvement (including genitals)	Mucosal surfaces (mouth and genitals)
Triggers (especially friction and trauma)	Percent of body surface area involvement
History of AIC	Leukotrichia
Family history of AIC	Trichrome vitiligo
Symptoms of thyroid disease	Koebner phenomenon
Symptoms of other AIC	Confetti-like depigmentation
Contraindications to light therapy (eg, photosensitive dermatoses, claustrophobia, or movement disorders)	Inflammatory lesions (erythema and scale)
Occupation	Stigmata of AIC (especially thyroid disease)
Ability to attend phototherapy	Halo nevi
Depression and quality of life	Repigmentation pattern

AIC, Autoimmune condition.

• **Vogt-Koyanagi-Harada syndrome is a rare presentation of vitiligo that also affects the hair, eye, inner ear, and brain**

Patients with vitiligo and their first-degree relatives have an increased prevalence of autoimmune thyroid disease, type 1 diabetes mellitus, pernicious anemia, rheumatoid arthritis, Addison disease, lupus, and Guillain-Barré syndrome, among others.^{7,45,46} The increased risk in family members for other autoimmune diseases suggests that genetic predisposition is for autoimmunity in general, rather than specifically for vitiligo. Melanocytes can be found in the uveal tract, retinal pigment epithelium, and membranous labyrinth of the inner ear. Therefore vitiligo, which may affect all melanocytes, may be associated with abnormalities in these organs. In 1 study, 27% of vitiligo patients had retinal pigment epithelium hypopigmentation,⁴⁷ while in another >30% had old chorioretinal scars.⁴⁸ Bilateral cochlear dysfunction has also been demonstrated in those with vitiligo.⁴⁹ Patients with a rare, severe form of vitiligo called Vogt-Koyanagi-Harada syndrome develop skin depigmentation and prominent leukotrichia, but only after presenting with flu-like symptoms, sound-induced ear pain, vertigo, hearing loss, meningitis, and symptomatic uveitis.⁵⁰ Alezzandrini syndrome is similar but even more rare, and consists of segmental vitiligo with leukotrichia, hearing loss, and visual changes.⁵¹ These diseases may be caused by an autoimmune attack on melanocytes in multiple tissues, which are normally present in all individuals but usually spared in vitiligo, possibly because of immune privilege in these organs. Of all conditions found in patients with vitiligo, thyroid disease is the most common

(prevalence ~19%),⁷ which has prompted some to advocate annual screening for disease through thyroid-stimulating hormone testing and autoantibody screening. A recent study estimated that the risk of developing autoimmune thyroid disease in patients with vitiligo doubles every 5 years, and screening every 3 years was recommended.⁵²

PATHOGENESIS

Key points

- **Vitiligo is an autoimmune disease of the skin that results in a loss of melanocytes**
- **Intrinsic defects in melanocytes may initiate disease through innate inflammation**
- **The interferon- γ -CXCL10 pathway plays a central role in driving autoimmunity in vitiligo**

Vitiligo pathogenesis involves intrinsic defects within melanocytes and autoimmunity that targets these cells.^{21,29,53-62} The production of melanin itself is toxic to melanocytes. First, the production of large amounts of protein increases the risk of misfolding of those proteins, which activates a stress pathway within the cell called the unfolded protein response. In addition, the energy requirements for protein production result in the generation of reactive oxygen species from mitochondrial energy metabolism. These 2 pathways appear to be hyperactivated in melanocytes from vitiligo patients, suggesting that these cells are less able to tolerate the demands of melanin production than those from healthy individuals.^{57,63} In fact, even healthy melanocytes develop cellular stress when exposed to specific chemical phenols, like monobenzyl ether of hydroquinone (MBEH).^{57,64,65} Once melanocytes

Table III. Differential diagnosis of vitiligo

Disorder	Clinical presentation	Diagnosis
Congenital conditions		
Piebaldism	Midline depigmentation; present at birth; lesions contain islands of normal pigment	Dominantly inherited; other affected family members
Waardenburg syndrome	White forelock, some with depigmented patches	Other stigmata of the syndrome, including hearing loss
Multiple ash leaf macules of TS	Multiple, well-demarcated, hypopigmented macules	Other cutaneous signs of TS, epilepsy, and other organ involvement
Hypomelanosis of Ito	Blaschkoid hypopigmentation present at birth	May or may not have other stigmata
Inflammatory conditions		
Pityriasis alba	Poorly demarcated hypopigmented macules; scale, erythema may be seen; most commonly in children with skin of color	Does not fluoresce with Wood's lamp; evidence of eczema may be noted
Postinflammatory hypopigmentation	Poorly demarcated hypopigmentation in an area of previous inflammation; may see primary dermatosis (eg, seborrheic dermatitis, eczema)	Decreased number of melanocytes with or without other inflammatory patterns
Lichen sclerosus et atrophicus	Typically on genitals; atrophic skin with or without fissures; figure-of-8 pattern surrounding vaginal introitus and anus	Lichenoid inflammation; epidermal atrophy; sparing of melanocytes
Discoid lupus erythematosus	Head, face, and neck erythematous, scaly macules and plaques with scarring, dyspigmentation and alopecia	Interface dermatitis with sparing of melanocytes
Hypopigmented sarcoidosis	Hypopigmented macules or patches; may be other manifestations of sarcoidosis	Histopathology reveals noncaseating granulomas
Cutaneous malignancy		
Mycosis fungoides (hypochromic variant)	Especially seen in skin of color; bathing suit distribution; with or without scale and signs of inflammation	Epidermotropism; atypical lymphocytes
Infections		
Acquired progressive macular hypomelanosis	Young adults; trunk (especially lower back and axillae)	Wood's lamp may reveal <i>Propionibacterium acnes</i> (pink fluorescence)
Tinea versicolor	Hypopigmentation; trunk	Positive skin scraping with potassium hydroxide preparation; green fluorescence of untreated lesions
Leprosy (tuberculoid or indeterminate)	Hypopigmented, hypoaesthetic white patches	Skin smear and biopsy specimen reveal <i>Mycobacterium leprae</i>
Pinta (late-stage)	Depigmented lesions, typically on distal extremities or other exposed part of the body	Rapid plasma reagin—positive; spirochetes on dark-field microscopy or histopathology
Exogenous causes		
Idiopathic guttate hypomelanosis	Exogenous ultraviolet light exposure causing nonprogressive 1-5 mm hypomelanotic macules in older adults; chronically sun-exposed sites; no leukotrichia	
Trauma-induced hypo- or depigmentation	Geometric shapes and history of trauma or surgical intervention	

Any single, unilateral lesion of these diagnoses could also be included on the differential diagnosis of segmental variant of vitiligo. TS, Tuberous sclerosis.

Table IV. Differential diagnosis of segmental vitiligo

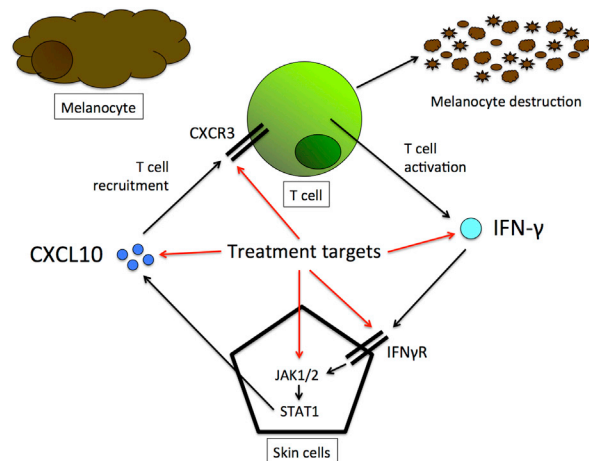
Disorder	Clinical presentation	Diagnosis
Nevus depigmentosus	At birth or first few years of life; grows in proportion to child; usually hypopigmented, has a jagged border, and lacks leukotrichia	Normal number of melanocytes histologically but decreased melanin
Nevus anaemicus	Presents at birth; mostly on the upper aspect of the chest; poorly demarcated white macule with surrounding erythema	Merges with surrounding skin with diascopy; no accentuation with Wood's lamp examination

become stressed, they release inflammatory signals that activate innate immunity, which may represent the initiating event in vitiligo.⁶⁴⁻⁶⁷

Studies report aberrant activation of innate immune cells in the skin of vitiligo patients, including recruitment of natural killer cells⁶⁸ and inflammatory dendritic cells,⁵⁹ suggesting that innate immune activation plays a role in the disease. Antigen-presenting cells probably migrate out of the skin to draining lymph nodes to present melanocyte antigens to T cells and activate them, thus serving to bridge cellular stress and adaptive T-cell responses. Innate cells may also locally secrete cytokines that recruit and activate autoreactive T cells, which then directly kill melanocytes.

Cytotoxic CD8⁺ T cells are both necessary and sufficient for melanocyte destruction in the skin of vitiligo patients, and therefore serve as the effector arm of autoimmunity in vitiligo.⁶⁹ Vitiligo patients have increased numbers of autoreactive melanocyte-specific, cytotoxic CD8⁺ T cells in their blood and skin,⁴⁰ and these can be seen infiltrating the epidermis in affected skin. In fact, the degree of CD8⁺ cellular infiltration correlates with disease severity.^{40,69-71} Specific antigens targeted by CD8⁺ T cells in vitiligo have been identified and primarily consist of proteins of the melanogenic pathway, such as gp100, MART1, tyrosinase, and tyrosinase related proteins 1 and 2.⁷⁰⁻⁷³

Interferon (IFN)- γ and IFN- γ -induced genes are the predominant cytokine pathway expressed in lesional skin,⁷⁴ and IFN- γ is required for the recruitment of melanocyte-specific, autoreactive CD8⁺ T cells to the skin.^{75,76} The IFN- γ -induced chemokine CXCL10 and its receptor CXCR3, which is expressed on autoreactive CD8⁺ T cells in blood and lesional skin from patients with vitiligo, appear to be critical for T cell recruitment in vitiligo.^{74,77,78} Blocking this pathway can both prevent vitiligo onset and reverse established disease in a mouse model. Therefore, interfering with this cytokine pathway may be a viable new treatment strategy (Fig 9).^{74,79} The expression of additional cytokines

**Fig 9.** Schematic diagram of current understanding of vitiligo pathogenesis.

has been reported in patients with vitiligo, including tumor necrosis factor- α , interleukin (IL)-6, and IL-17; however, their functional role, if any, is unclear. In fact, patients taking biologics that block tumor necrosis factor- α , IL-12/23, and IL-17 for other diseases have been reported to develop de novo vitiligo or have exacerbated disease.⁸⁰⁻⁸³

In addition to the pathogenic role of cytotoxic, autoreactive CD8⁺ T cells in vitiligo, CD4⁺ T regulatory cells (Tregs) appear to play an important role in preventing and controlling disease. Patients with immune polyendocrinopathy and X-linked syndrome, who lack Tregs, are at increased risk for vitiligo.⁸⁴ A recent study reported that melanocyte-specific, autoreactive CD8⁺ T cells from healthy patients exhibit a phenotype that reflects ongoing Treg-mediated control, while vitiligo patients possess cells that appear to be more activated and lack this phenotype.⁸⁵ However, it is currently unclear whether Treg numbers are normal or fewer, whether they have impaired homing to the skin, and whether or not they are functionally altered in vitiligo patients.⁸⁶⁻⁹⁰ Future studies are required to identify how Tregs function within the skin and exactly how they are defective in human patients with vitiligo.

Some have postulated a role for the nervous system in vitiligo pathogenesis, which is referred to as the “neural hypothesis.” However, the primary basis for this hypothesis is the unilateral distribution pattern of segmental vitiligo,⁹¹ which led to its being labeled “dermatomal vitiligo.” Close observation reveals that the distribution is rarely, if ever, dermatomal.^{92,93} Therefore, based on this misidentification and much better supported alternatives, we agree with Ortonne et al⁹¹ that the hypothesis is still without sufficient evidence. In addition, a recent case report revealed that segmental vitiligo exhibits melanocyte-specific T-cell infiltration with an interface dermatitis that is identical to common vitiligo,⁹⁴ suggesting that it is also mediated by autoimmunity.

The pathogenesis of segmental vitiligo has recently been hypothesized to include melanocyte mutations that occur during embryologic development, a process called somatic mosaicism.⁹⁵ A single mutation in an embryonic melanocyte would be passed on to its daughter cells, which later differentiate into functional melanocytes in the epidermis of the individual. This would result in a unilateral distribution of abnormal melanocytes in a pattern distinct from dermatomes, because melanocytes migrate from the neural crest ventrally in paths that are independent from cutaneous nerves.⁹⁵ Based on the fact that intrinsic melanocyte abnormalities contribute to the pathogenesis of vitiligo, it is possible that somatic mutations within stress pathways could contribute to this unilateral manifestation of vitiligo. Then, consistent with the known pathogenesis of vitiligo, these abnormalities may initiate autoimmunity that is limited to the segment of altered melanocytes, sparing normal cells elsewhere. The local field of abnormal melanocytes could explain why segmental vitiligo is resistant to medical treatments but so responsive to surgical ones (discussed in more detail in the second article in this continuing medical education series), because abnormal melanocytes may have difficulty repigmenting the lesions but surgical approaches successfully transplant normal melanocytes to the affected areas, enabling long-term improvement. Additional studies will be required to test this hypothesis and determine whether somatic mutations exist within melanocytes targeted in segmental vitiligo.

RISK FACTORS

Key points

- **Genetics strongly influence the risk of developing disease**
- **Environmental factors also contribute, including exposure to phenolic compounds found in household products**
- **Nonspecific induction of skin inflammation may induce local vitiligo lesions**

The risk of developing vitiligo is 0.5% to 2% in the general population, approximately 6% when a first-degree relative is affected, and 23% when an identical twin is affected,⁷ suggesting that genetic factors are important elements in developing disease. However, not all identical twins are affected, and therefore nonheritable factors must also play a role, which may indicate a role for exposures in disease pathogenesis, broadly characterized as “environmental factors.”

Genetics

Vitiligo is inherited in a polygenic pattern, suggesting that multiple alleles contribute to the genetic risk for disease. Indeed, a series of genome-wide association studies and genetic linkage studies have implicated approximately 50 genetic loci as important factors that contribute to vitiligo risk.⁹⁶ The overwhelming majority of these genes are immune genes, confirming a critical role for the immune system in vitiligo pathogenesis. Some are known to play a role in innate immunity (*IFIH1*, *CASP7*, *NLRP1*, *TICAM1*, and others), while others are key factors in mediating adaptive immunity (*CTLA4*, *CD80*, *HLA*, *GZMB*, *FOXP3*, and others), confirming a need for both arms of the immune system as discussed above. In addition to immune genes, a small subset of risk alleles is only expressed in melanocytes (*TYR*, *OCA2*, and *MC1R*), supporting a role for melanocytes in initiating disease. In addition, *XPB1* has also been implicated and is a key component of the unfolded protein response cellular stress pathway, which may also be important in initiating inflammation.^{96,97} Additional studies through functional genomics will be required to determine the specific roles that each gene plays in driving vitiligo pathogenesis.

Environmental triggers

The first environmental exposure connected to vitiligo was identified in 1939, when a large number of factory workers developed depigmentation on their hands and remote locations that was caused by the presence of MBEH in their gloves.⁹⁸ MBEH is so effective at promoting depigmentation in vitiligo that it is now used to accelerate depigmentation in those with severe disease, resulting in even skin tone.^{99,100} A more recent “outbreak” of vitiligo cases (>16,000 cases) was reported in the summer of 2013 in Japan and was determined to be caused by the use of a new skin-lightening agent that contained rhododendrol as the active ingredient.^{101,102} Additional chemicals implicated as inducers of vitiligo include 4-tert-butylphenol and 4-tert-butylcatechol, which can be found in adhesive resins, industrial oils,

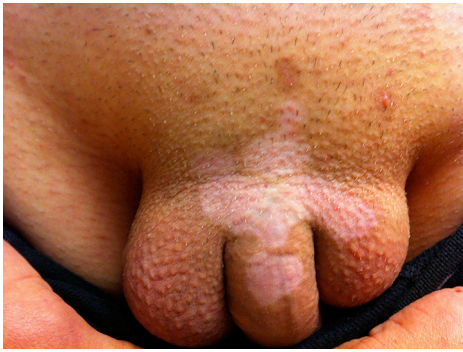


Fig 10. Vitiligo in an area of imiquimod application.

paints, adhesives, and other products.^{103,104} A common feature of these chemicals is that all are phenols, bearing a benzene ring with an attached hydroxyl group, which is similar to the amino acid tyrosine, also a phenol. Their mechanism of action appears to be that they act as tyrosine analogs, interfering with tyrosinase and melanin synthesis, inducing additional stress in melanocytes, and resulting in the release of inflammatory factors that initiate autoimmune attack on the melanocytes.^{23,57,62,65} However, only a subset of exposed patients appears to be susceptible to depigmentation, as not all those exposed to the chemicals get the disease. The rhododendrol exposure in Japan only affected about 2% of users,¹⁰⁵ suggesting that exposures act on genetically susceptible patients to induce disease.

Recently, Wu et al¹⁰⁶ reported that use of permanent hair dyes increase the risk of developing vitiligo. In this study, even “having ever used” hair dyes increased a woman’s risk of developing vitiligo, and this was increased further with first use before 30 years of age and with longer duration of use. Hair dyes contain multiple phenol ingredients, but the exact chemical ingredients responsible for inducing vitiligo is currently unknown. Additional products implicated in a retrospective study based on patient recall (and therefore susceptible to recall bias) include detergents, topical dyes, and others.²²

Vitiligo patients are susceptible to skin trauma through the Koebner phenomenon.¹⁰⁷ In addition, imiquimod-induced vitiligo has been reported in patients treated for genital warts, condyloma acuminata, extramammary Paget disease, and basal cell carcinoma¹⁰⁸⁻¹¹⁰ (Fig 10), and others have reported depigmentation at the site of IFN- α injection for the treatment of hepatitis C.¹¹¹ Both skin trauma and imiquimod exposure induce IFN- α/β in the skin,^{110,112} and therefore depigmentation in these cases may be caused by the ability of IFN- α/β to also induce CXCL10¹¹³ which, as

discussed above, promotes the migration of melanocyte-specific, autoreactive T cells into the skin in vitiligo.⁷⁴

In summary, vitiligo is a common skin disease with a large potential impact on patients’ quality of life, and therefore it should not be dismissed as “simply cosmetic.” Distinct subtypes of vitiligo and lesion patterns are important to recognize because they influence prognosis through disease activity, progression, and treatment responses. A variety of other autoimmune diseases are associated with vitiligo, and recognizing this association will help to guide workup and clinical management. Recently, much has been revealed about the pathogenesis of vitiligo and risk factors for disease, which may lead to improved prevention and treatment options.

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