



Vitiligo

EPIDEMIOLOGY

Vitiligo occurs worldwide, with a prevalence of 0.1 percent to 2.0 percent. In the United States, the estimated incidence is 1 percent. Vitiligo commonly begins in childhood or young adulthood, with peak onset of 10 to 30 years, but it may occur at any age. All races are affected, and both sexes are equally afflicted. A female preponderance has been reported, but the discrepancy has been attributed to a presumed increase in reporting of cosmetic concerns by female patients. Although familial clustering of cases is commonly seen, inheritance occurs in a non-Mendelian pattern. Approximately 20 percent of patients with vitiligo have at least one first-degree relative with vitiligo, and the relative risk for first-degree relatives of vitiligo patients is increased by 7- to 10-fold.

ETIOLOGY AND PATHOGENESIS

Vitiligo is a multifactorial polygenic disorder with a complex pathogenesis. Although several theories have been proposed to explain the loss of epidermal melanocytes in vitiligo, the precise cause remains unknown. Considerable progress has been made, however, over the last two decades. Theories include autoimmune, cytotoxic, biochemical, oxidant-antioxidant, neural, and viral mechanisms for destruction of epidermal melanocytes. Several studies also point to a significant role of genetic susceptibility to vitiligo.

Genetics of Vitiligo

Vitiligo is characterized by incomplete penetrance, multiple susceptibility loci, and genetic heterogeneity. The inheritance of vitiligo may involve genes associated with melanin biosynthesis, response to oxidative stress, and regulation of autoimmunity.

The frequent association of vitiligo with autoimmune diseases prompted investigations of possible HLA associations in vitiligo. HLA types associated with vitiligo in more than one study include A2, DR4, DR7, and Cw6.

Autoimmune Hypothesis and Humoral Immune Response

The association of vitiligo with autoimmune conditions is well established. Thyroid disorders, particularly Hashimoto thyroiditis and Graves disease, are commonly associated with vitiligo, along with other endocrinopathies such as Addison disease and diabetes mellitus. Alopecia areata, pernicious anemia, systemic lupus erythematosus, inflammatory bowel disease, rheumatoid arthritis, psoriasis, and autoimmune polyglandular syndrome are other associated disorders, but the significance of some of these associations is debated.

The most convincing evidence of an autoimmune pathogenesis is the demonstration of circulating autoantibodies in patients with vitiligo.

The question has been raised whether vitiligo antibodies are present as a result of pigment cell destruction, as an epiphenomenon, or if these antibodies cause destruction of pigment cells. Support for the latter possibility comes from animal studies in which pigment cell antibodies appear before the onset of pigment loss.

Smyth Chicken Model

Aberrant processes involved in the pathogenesis of vitiligo have been studied using animal models. The mutant Smyth line chicken is a well-studied animal model for autoimmune vitiligo. The hypomelanosis that develops in the feathers and ocular tissue of the birds is similar to vitiligo in humans.¹⁰ Murine, equine, and porcine models of vitiligo have also been described.^{10, 11}

Cellular Immune Mechanisms

In addition to the involvement of humoral immune mechanisms in the pathogenesis of vitiligo, there is strong evidence indicating cellular immune processes. Destruction of melanocytes may be directly mediated by autoreactive cytotoxic T cells. An increased number of circulating CD8⁺ cytotoxic lymphocytes reactive to MelanA/Mart-1 (melanoma antigen recognized by T cells), glycoprotein 100, and tyrosinase has been reported in patients with vitiligo.⁷

Activated CD8⁺

T cells have been demonstrated in perilesional vitiliginous skin.¹²

Interestingly, the melanocyte-specific T-cell receptors found in melanoma and vitiligo patients are structurally very similar. Given the potential therapeutic implications for melanoma, studies looking at the similarities between melanoma and vitiligo are currently areas of active investigation. Research has already led to the application of immunization strategies, such as induction of tumor-specific T cells for prevention and eradication of cancer.

Disturbance in the Oxidant-Antioxidant System in Vitiligo

Oxidant stress may also play an important pathogenic role in vitiligo. Several studies validate a possible oxidant stress theory, which suggests that accumulation of free radicals toxic to melanocytes leads to their destruction. Increased nitric oxide levels have been demonstrated in cultured melanocytes and in the serum of patients with vitiligo, suggesting that nitric oxide could lead to autodestruction of melanocytes.

Neural Theory

Segmental vitiligo frequently occurs in a dermatomal pattern, leading to a neural hypothesis that proposes certain chemical mediators released from nerve endings cause decreased melanin production.

Viral

Convergence Theory

Together, available data suggest that vitiligo is multifactorial and may be the end result of several different pathologic pathways. Experts concur that vitiligo may be a syndrome rather than a single disease.

CLINICAL FINDINGS

Patients with vitiligo present with one to several amelanotic macules that appear chalk- or milk-white in color. The lesions are usually well-demarcated, but the margins may be scalloped. They are accentuated on Wood's lamp examination. Lesions enlarge centrifugally at an unpredictable rate and can appear on any body site, including mucous membranes. However, initial lesions occur most frequently on the hands, forearms, feet, and face. When vitiligo occurs on the face, it often favors a perioral and periocular distribution.

Classification of Vitiligo

Vitiligo is classified as segmental, acrofacial, generalized, and universal, or by pattern of involvement as focal, mixed, and mucosal types.

Koebnerization commonly occurs in vitiligo. Lesions frequently develop at sites of trauma, such as mild friction from clothes, or from a cut, burn, or abrasion .

Depending on ethnic color, vitiligo is more or less conspicuous .

Clinical Variants

Trichrome vitiligo is characterized by both depigmented and hypopigmented macules in addition to normally pigmented skin. The natural evolution of the hypopigmented areas is progression to full depigmentation. Quadrichrome vitiligo refers to the additional presence of marginal or perifollicular hyperpigmentation. This variant is recognized more frequently in darker skin types, particularly in areas of repigmentation. Cases of pentachrome vitiligo have also been reported with additionally blue-gray hyperpigmented macules, representing areas of melanin incontinence (dermal melanin). Occasionally, patients with vitiligo may present with an unusual variant called the confetti type or vitiligo punctue. These patients have several tiny, discrete hypomelanotic macules. Inflammatory vitiligo is characterized clinically by erythema at the margins of vitiligo macules.

RELATED PHYSICAL FINDINGS

Associated Disorders

Vitiligo is frequently associated with disorders of autoimmune origin. The most prevalent associated endocrinopathy is thyroid dysfunction, either hyperthyroidism (Graves disease) or hypothyroidism (Hashimoto thyroiditis). Vitiligo usually precedes the onset of thyroid dysfunction. Addison disease, pernicious anemia, alopecia areata, and diabetes mellitus also occur with increased frequency in patients with vitiligo. Patients with autoimmune polyendocrinopathy candidiasisectodermal dystrophy have an increased prevalence of vitiligo. Mutation of the AIRE (autoimmune regulator) gene has been identified in this syndrome. Patients should be questioned about symptoms for these disorders.

Vitiligo may affect active melanocytes throughout the body, including pigment cells present in hair, the inner ear, and the retina. Poliosis (leukotrichia) occurs in many patients. Premature graying has been reported in vitiligo patients and in their close relatives. Auditory and visual disturbances are present in some patients. Aseptic meningitis may rarely result from destruction of leptomeningeal melanocytes.

Differential Diagnosis of Vitiligo (Site Specific)

Most Likely

- • Face
 - 1. o Tinea versicolor
 - 2. o Pityriasis alba
 - 3. o Post-inflammatory hypopigmentation
- • Anogenital area
 - 1. o Lichen sclerosus et atrophicus

Consider

- . Face

1. o Chemical leukoderma
2. o Sarcoidosis

- . Hands

1. o Chemical leukoderma

Vitiligo-like depigmentation can occur in patients with malignant melanoma and is believed to result from a T-cell-mediated reaction to antigenic melanoma cells, with cross-reaction to normal melanocytes. Such depigmentation has also been observed during the course of autologous T-cell-based immunotherapy of melanoma. Depigmentation in this setting may portend a better prognosis. Amelanosis around primary tumors may resemble a halo nevus, but vitiligo-like depigmentation can also occur at sites remote from the melanoma.

OCULAR DISEASE

Although patients with vitiligo do not usually have ophthalmologic complaints, they can have several ocular findings. Pigmentary abnormalities of the iris and retina may occur. Choroidal abnormalities have been reported in up to 30 percent of patients and iritis in approximately 5 percent. Uveitis can be a frequent ocular manifestation. Exophthalmos may occur in the setting of concomitant Graves disease. Visual acuity is generally not affected.

VOGT-KOYANAGI-HARADA SYNDROME

The Vogt-Koyanagi-Harada syndrome (VKH) consists of vitiligo in association with uveitis, aseptic meningitis, dysacusis, tinnitus, poliosis, and alopecia. It is a rare, systemic, T-cell-mediated autoimmune disorder. VKH syndrome is associated with other autoimmune disorders such as autoimmune polyglandular syndrome, hypothyroidism, Hashimoto thyroiditis, and diabetes mellitus. VKH syndrome classically occurs in three phases. During the first phase, the meningoencephalic phase, patients may have headache, meningismus, seizures, muscle weakness, or paralysis after a prodrome of fever, malaise, nausea and vomiting. Subsequently,

the acute ophthalmic phase occurs when patients may develop photophobia, eye pain, and altered visual acuity. Patients may develop uveitis, iridocyclitis, choroiditis, and retinal detachment during this phase and can later develop complications such as cataracts and glaucoma. Vitiligo, alopecia, and poliosis²² usually follow, but can occur before the other manifestations.

ALEZZANDRINI SYNDROME

The constellation of clinical findings in Alezzandrini syndrome includes facial vitiligo, poliosis, deafness, and unilateral tapetoretinal degeneration. The etiology remains poorly understood, but as in vitiligo and VKH syndrome, autoimmune processes are thought to be involved. Only a few cases have been reported since the first description of a patient with vitiligo, poliosis, and unilateral retinitis in 1959.²³

Laboratory Tests

The diagnosis of vitiligo is primarily based on clinical examination. However, given the association between vitiligo and other autoimmune diseases, several screening laboratory tests are helpful, including thyroid stimulating hormone level, antinuclear antibody, and complete blood count. Clinicians should also consider investigating for serum antithyroglobulin and antithyroid peroxidase antibodies, particularly when patients have signs and symptoms of thyroid disease. Antithyroid peroxidase antibodies, in particular, are regarded as a sensitive and specific marker of autoimmune thyroid disorders.

Histology

By definition, vitiligo lacks melanocytes in lesional skin. As well, a superficial dermal, perivascular and perifollicular primarily lymphocytic infiltrate may be observed at the margin of vitiliginous lesions and in early lesions, consistent with cell-mediated immune processes destroying melanocytes in vitiligo.

□ PROGNOSIS AND CLINICAL COURSE

The prognosis and course of vitiligo are unpredictable. Initial clinical sub-type of vitiligo does not predict future anatomical sites of involvement or activity of disease.

TREATMENT

There are many different treatment options available for patients with vitiligo . Most therapies are intended to restore pigment to the skin. All approaches have advantages and disadvantages; and none is appropriate for every patient with vitiligo.

Sunscreens

Sunscreens help prevent sunburn and thus may lessen photodamage as well as the chance that a Koebner phenomenon will occur. Sunscreens also decrease tanning of the uninvolved skin and therefore lessen the contrast with vitiliginous lesions.

Cosmetics

Many patients, especially patients with focal vitiligo, find cosmetic cover-ups to be a valuable treatment option. Areas of leukoderma, especially on the face, neck, or hands can be covered with conventional make-up, self-tanning products, or other topical dyes . Cosmetics offer limited cost, minimal side effects, and the ease of application. As well, many of the cover-ups can be individualized to obtain an exact color match to the patient's normal skin.

Topical Corticosteroids

Topical corticosteroids are indicated for the treatment of limited areas of vitiligo and are often the first line of therapy for children, although most experience is anecdotal. Lesions on the face appear to have the best response to topical corticosteroids; lesions on the neck and extremities (with the exception of the fingers and toes) also have a favorable response.²⁵ It is not known why lesions on the face have a better response rate. Possible explanations include a high permeability of the facial skin to the corticosteroids, a larger number of residual melanocytes in the uninvolved facial skin, greater follicular reservoirs, or melanocyte damage that is more easily reversed. Lesions on the face often re-pigment diffusely whereas a dot-like follicular pattern of repigmentation is more common elsewhere.

Localized lesions can be treated with a high-potency fluorinated corticosteroid for 1 to 2 months, after which prudence dictates that therapy is gradually tapered to a lower-potency corticosteroid. In children and patients with larger lesions, a medium potency non-fluorinated corticosteroid is often used, likely at the expense of efficacy. Caution must be used when using topical steroids on and around the eyelids, as their use can increase intraocular pressure and exacerbate glaucoma.

Treatments for Vitiligo

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TOPICAL

PHYSICAL

SYSTEMIC

SURGICAL

First line

Corticosteroids

Ultraviolet B (narrow band)

Calcineurin inhibitors

Systemic psoralen and ultraviolet A light

Second line

Calcipotriol

Topical psoralen and ultraviolet A light
Excimer laser

Corticosteroids (pulse therapy)

Grafting
Melanocyte transplant

Wood's lamp examination can be used to monitor response to treatment. If no response is seen by 3 months, therapy should be discontinued. Maximum repigmentation may take 4 months or longer (there is a 30 percent to 40 percent response rate with 6 months of corticosteroid use). More darkly pigmented patients often have a more favorable response to topical corticosteroids than those with lighter complexions. The ease of application, high rate of compliance, and limited cost are the benefits of topical corticosteroid therapy for treating limited vitiligo. Recurrence after cessation of treatment and corticosteroid side effects (skin atrophy, telangiectases, striae, and, rarely, contact dermatitis) are the limiting factors. All patients, particularly children, should be monitored closely, for these potential side effects.

Topical Immunomodulators

Topical tacrolimus ointment 0.03 percent to 0.1 percent is effective in repigmentation of vitiligo

when applied twice daily in patients with localized disease, particularly on the face and neck. It is reported to be more effective when combined with ultraviolet B (UVB) or excimer (308 nm) laser therapy. Tacrolimus ointment is generally considered safer for children than topical steroids.

Topical Calcipotriol

Topical calcipotriol 0.005 percent produces cosmetically acceptable repigmentation in some patients with vitiligo. It can be combined with topical corticosteroids in adults and children to give possibly faster onset of repigmentation with better stability of achieved pigmentation.

Pseudocatalase

Catalase, an enzyme normally found in skin that decreases damage from free radicals, has been reported to be low in the skin of vitiligo patients. A replacement therapy using an analog of normal human catalase (pseudocatalase) in combination with narrowband UVB (NB-UVB) phototherapy has been reported in uncontrolled trials to re-pigment some vitiligo patients and prevent progression of disease.

Systemic Therapies

Systemic immunosuppressive drugs have many potential side effects that are difficult to justify for a disease such as vitiligo. However, systemic corticosteroids have been used as pulse therapy with variable results and may prevent rapid depigmentation in active disease.

Psoralen and Ultraviolet A Therapy

Topical or oral 8-methoxypsoralen combined with UVA (320 to 400 nm) irradiation (PUVA) is effective for treating vitiligo although frequent treatments over many months are required . After exposure to UVA, psoralens covalently bind to DNA and inhibit cell replication. How this then

leads to repigmentation of vitiligo areas is not well understood. PUVA stimulates tyrosinase activity (an essential enzyme in melanin synthesis) and melanogenesis in unaffected skin. PUVA is also locally immunosuppressive, and decreased expression of vitiligoassociated melanocyte antigens has been reported.

In vitiligo, melanocytes in the bulb and infundibulum of the hair follicle are

often destroyed; but the lower and middle portions of the follicle as well as the outer root sheath are spared. PUVA stimulates follicular melanocytes to migrate into the epidermis and repopulate the surrounding depigmented skin, possibly as a result of the release of cytokines and chemotactants from the epidermal keratinocytes .

Topical PUVA is sometimes used in patients whose vitiligo involves less than 20 percent of the body surface area . However, unwanted side effects are common and include cosmetically displeasing hyperpigmentation of skin surrounding vitiligo areas due to inadvertent psoralen application, severe phototoxicity reactions, and intense pruritus. Oral psoralens are used for patients with more extensive involvement or in patients who do not respond to topical PUVA .

It is important to select vitiligo patients carefully for PUVA therapy. Although 70 percent to 80 percent of patients experience some repigmentation with PUVA, fewer than 20 percent of patients totally re-pigment. In general, vitiligo on the trunk, proximal extremities, and face respond well to PUVA, but lesions on the distal extremities respond poorly. As with corticosteroids, patients with a darker complexion tend to respond better to PUVA, possibly because they tolerate higher PUVA exposures. Potential side effects of PUVA .

Narrowband Ultraviolet B Radiation

NB (311 nm)-UVB irradiation is another option for patients with vitiligo and is considered by many to be the first choice for most patients. In patients with extensive generalized vitiligo, NB-UVB therapy was more effective than topical PUVA (67 percent versus 46 percent response rate, respectively;). If no improvement is seen within 6 months of treatment, NB-UVB therapy should be abandoned. In one study, 53 percent of children experienced more than 75 percent repigmentation after NB-UVB therapy and 6 percent showed complete repigmentation. Again,

better pigmentation was achieved on the face, trunk, and proximal extremities than with the distal extremities and groin.

Excimer Laser

Excimer (308 nm) laser has been recently studied in several trials for its efficacy in treating vitiligo. It has been found to be most effective when treatments are given three times weekly, with treatment periods of more than 12 weeks necessary to obtain satisfactory repigmentation. The initial dose is 50 to 100 mJ/cm². As with standard phototherapy, excimer laser produces the best treatment results on the face; the least responsive areas are the hands and feet.

57-63

Depigmentation

Monobenzyl ether of hydroquinone (Monobenzone) is the only agent available in the United States and Europe for depigmenting residual normal skin in patients with extensive vitiligo. Monobenzone is a phenolic toxin that destroys epidermal melanocytes after protracted use. Monobenzone can therefore produce a uniform depigmented state that is cosmetically more acceptable for many patients than the contrast between normal and affected skin . Monobenzone is available as a 20 percent cream and can be formulated at concentrations up to 40 percent. The individual using monobenzone should avoid direct contact with others for 1 hour after application, as contact may cause depigmentation of others' skin. Monobenzone may also be irritating and allergic sensitization may occur.

Autologous Thin Thiersch Grafting

Thin split-thickness grafts in the treatment of vitiligo are obtained using scalpel or dermatome and are placed onto recipient sites prepared in a similar manner or by dermabrasion. Achromic areas ranging in size from 6 to 100 cm² can be treated. Recently, the technique of thin split-thickness grafts has been modified for the treatment of vitiligo with the harvesting of grafts by mechanical dermatome, which has shown excellent results. This technique has also been used to successfully treat vitiligo of the lip. The advantage of this technique is that it allows the grafting of large areas in a relatively short time. However, this must be weighed against the need for general anesthesia and the risk of hypertrophic scarring of both donor and recipient

sites.

65-67

Suction Blister Grafts

Separation of viable epidermis from dermis can be accomplished through the production of suction blisters that separate skin immediately above the dermal-epidermal junction. This is adapted to the treatment of vitiligo; pigmented epidermis is harvested by this technique and is used to cover achromic areas that have been prepared by denuding them with liquid nitrogen blisters. Melanocytes are contained within the epidermal roof of 2.0- to 2.5-cm suction blisters. The tops of these blisters are removed and are directly applied to the denuded area of achromic skin. Pigmentation usually develops in 3 to 6 months. There may be areas of achromic fissures between grafts in the recipient areas. An advantage of suction blister grafts is that scarring is minimal, as the dermis is left intact in both donor and recipient sites. However, most physicians do not have the mechanical apparatus needed for the production of the blisters at the donor site.

Autologous Mini-Punch Grafts

The autologous mini-punch grafts technique uses 1.20- to 1.25-mm full-thickness punch grafts placed 4 to 5 mm apart onto comparably sized recipient sites . This graft size was found to minimize both the “cobblestoning” (trap door) effect and the cosmetic damage to the donor site that is especially prominent with larger-sized grafts, yet it also contained enough melanocyte sources to stimulate the spotty perifollicular repigmentation .

Transplantation of Cultured Autologous Melanocytes

The technique of transplanting melanocyte-containing cultures of cells has the theoretic advantage of potentially treating large areas using cells harvested from a small piece of donor skin by expanding the melanocyte population in vitro. Its major disadvantage lies in the complexities and cost of the culture systems. As well, there is concern about what, if any,

effects the additives required for culturing the cells have on the melanocytes and, subsequently, on the patient. Melanocytes can be cultured more readily in the presence of keratinocytes, and co-cultures can be used to re-pigment areas of skin depigmented by disease or injuries. In the United States, these techniques now require that the cultures be performed using Good Manufacturing Practices, a

very regulated and expensive approach available at very few academic centers .

PREVENTION

No therapy prevents vitiligo from developing in patients. However, systemic steroids or topical pseudocatalase may slow depigmentation in some patients with active disease.