Vitiligo

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SUMMARY

Vitiligo represents a selective destruction of the melanocytes. It is a relatively common, probably autoimmune disorder that affects people of all backgrounds and both genders. No particular group seems to be preferentially affected. Half of vitiligo patients have an onset before the age of 18 years. In regions where leprosy is endemic, individuals with vitiligo are often stigmatized due to similarities in appearance between the two diseases. We will review this important subject, emphasizing the latest therapeutic advances.

KEY WORDS

depigmenting disorders, vitiligo, autoimmunity

Introduction

In vitiligo the selective destruction of the skin melanocytes results in the development of unsightly depigmented patches. The disease can have devastating consequences on an individual's relationships with others and internal feelings of self-worth. Fifty percent of vitiligo patients experience disease onset before the age of 18 when they are most concerned about their appearance, and self-image is the most fragile (1,2). Additionally, in regions where leprosy is endemic, individuals with vitiligo are stigmatized due to similarities in appearance between the two diseases. Fortunately, advances in our understanding and management of vitiligo are reducing its effect on the millions of individuals afflicted.

Clinical description

Vitiligo is a depigmentation disorder affecting between 1% and 2% of the general population without any racial, sexual or regional differences in prevalence. Vitiliginous patches contain either reduced melanin or no pigment at all. Initially small, they may enlarge and coalesce into larger patches (see figure 1). Lesions on the face, back of hands, wrists, in the axillae or umbilicus are especially prominent. Vitiligo is most striking around the body orifices: eyes, nostrils, mouth, nipples, umbilicus and genitalia. Obviously, the disease is more noticeable in environments where there is increased contrast with the surrounding skin. This can be observed with dark-complexioned patients and patients who become tanned, as vitiliginous patches do not tan in

Table 1. Segmental versus nonsegmental vitiligo.

	Nonsegmental	Segmental
Prevalence	72-95%	5-28%
Distribution	Symmetrical, non-dermatomal	Unilateral, dermatomal
Onset	Any age	Early
Course	Variable rate of growth with new lesions throughout life	Rapid initial growth with non-progression within 2 years
Etiology (most plausible)	Autoimmune	Neurochemical
Koebnerization	Frequent	Rare
Autoimmune association	Strong	Rare

response to ultraviolet light. Additionally some lesions have a tendency to be surrounded by hyperpigmented skin. Clinical course and treatment of vitiligo differ depending on the type of vitiligo.

Vitiligo can be separated into segmental and nonsegmental types (Table 1) (2). In *nonsegmental vitiligo,* there is usually symmetric distribution of lesions and new patches may appear throughout the patient's life. It may be either generalized or localized. In generalized, nonsegmental vitiligo there is usually widespread distribution of depigmented patches. Vitiligo so extensive that few normally pigmented patches remain is known as *vitiligo universalis*. Acrofacial vitiligo skin involvement is limited to the distal digits and periorificial facial areas. *Focal vitiligo* lesions are limited in quantity and location and have a non-dermatomal distribution (see Figure 1). Focal vitiligo may develop into generalized vitiligo or may follow an early-stabilizing clinical course (3). *Segmental vitiligo* has important differences in etiology, prevalence of associated illnesses and therapy compared to other forms of vitiligo. It usually has unilateral involvement and a dermatomal distribution. Segmental vitiligo is known for its early onset and rapid spread. Without treatment, lesions are typically persistent throughout life, but stop developing within two years of onset. Childhood vitiligo, in one survey, consisted primarily of typical generalized, nonsegmental vitiligo (78%), with focal vitiligo (14.4%) and segmental vitiligo (4.6%) being far less prevalent (4).

There are a number of variations of the presentation of vitiligo (1,2). If, in addition to normally pigmented and amelanotic skin, there is also an intermediate, hypopigmented interface, the patient is said to have trichrome vitiligo. Quadrachrome vitiligo describes the presence of a fourth, hyperpigmented band, which may develop during repigmentation. When vitiligo macules develop at sites of post-inflammatory hypermelanosis, "blue vitiligo" is observed. In inflammatory vitiligo, the depigmented macule is surrounded by a raised, erythematous border and sun exposure may cause the whole macule to become erythematous. Confetti vitiligo describes a condition where a patient develops as many as several hundred small macules (less than or equal to 2 mm) with variable distribution patterns.

Genetics

The earliest evidence suggesting a genetic basis for vitiligo was its association with a number of other autoimmune disorders known to have heritable predispositions, such as diabetes mellitus. Genetic diseases are substantially more prevalent in children of parents who are close relatives. A study conducted in Bangalore, India, a community where consanguineous marriages are common, reported that as many as 20% of the population developed depigmented lesions (5). Additionally, in patients with nonsegmental vitiligo, a significantly earlier onset has been observed when there is a family history of vitiligo (on average, 24.8 versus 42.2 years) (6). Genetic models suggested by analysis of family studies include a *multifactorial model* (7), *a dominant model with incomplete penetration* (8), and a *multilocular recessive model* (9). A more recent study suggests that there may in fact be two coexisting modes of inheritance for vitiligo depending on age of onset (10). In patients with early onset vitiligo (before the age of 30), vitiligo inheritance most closely followed a dominant mode of inheritance with incomplete penetration. However, a predisposition to vitiligo resulting from a recessive genotype and exposure to certain environmental triggers appeared to explain the inheritance pattern of late onset vitiligo (after 30 years of age). Specific HLA haplotypes are strongly associated with vitiligo family history, severity of disease, age of onset and population geography (11-13).

Gene polymorphisms in the MHC Class II region of the HLA locus have been previously found to be associated with other autoimmune diseases, such as type 1 diabetes mellitus and juvenile-onset rheumatoid arthritis (14,15). The HLA genes encoding both the transporter associated with antigen-processing (TAP1) and subunits of the immunoproteasome (LMP2/LMP7) have recently been found to be associated with vitiligo of

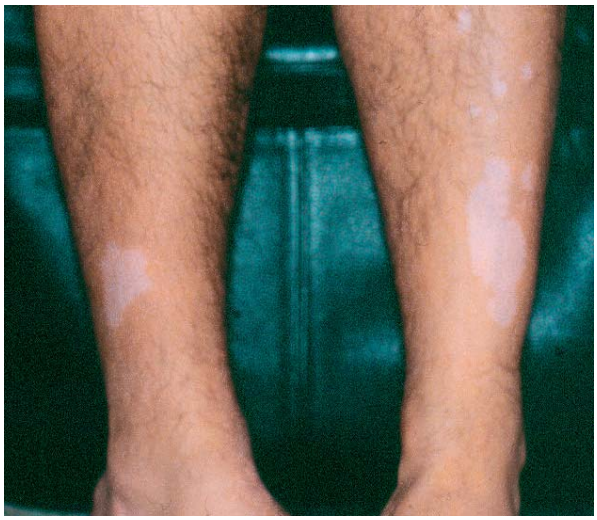

Figure 1. 33 year-old patient with depigmented patches on the anterior portions of his legs.

early onset in Caucasian patients (16). The cytotoxic lymphocyte antigen 4 (CTLA-4) gene encodes a protein involved in the inhibition of improperly-activated T-cells. CTLA-4 variants have been linked to numerous autoimmune diseases. Recently, a study comparing 100 United Kingdom patients with vitiligo to controls found an association between the CTLA-4 polymorphism and vitiligo when it occurred with other autoimmune diseases, though not isolated vitiligo (17). Catechol-O-methyl transferase (COMT) is an enzyme that plays a major role in the metabolism of toxic or biologically active drugs, neurotransmitters and metabolites. One such metabolite, O-quinones, can be formed during melanin synthesis in the absence of adequate COMT activity. A COMT polymorphism has been found to be significantly associated with acrofacial vitiligo (18). Chromosome 1p31, termed the autoimmune susceptibility locus (AIS1), has been found to be associated to a highly significant degree with generalized vitiligo in North American and United Kingdom whites (19). Reduced activity of the VIT1 gene, located on chromosome 2p16, has been associated with increased susceptibility to vitiligo, possibly as a result of decreased melanocyte nucleotide mismatch repair (20).

Systemic associations

Nonsegmental vitiligo is associated with a number of immune system aberrations. The presence of organ-specific autoantibodies in the serum of vitiligo patients has been well-established in adults as well as children (21,22). Childhood, nonsegmental vitiligo is frequently associated with autoimmune thyroiditis (23). Aside from this, children with vitiligo are usually healthy (24,25). To the contrary, vitiligo in adults is quite strongly associated with a number of autoimmune disorders, including alopecia areata, diabetes mellitus, pernicious anemia, Addison's disease, and Hashimoto's thyroiditis (26,27). As in children, the strongest association in adults is found with autoimmune thyroiditis, with a prevalence of 30% among vitiligo patients (24) compared to 10 % prevalence in the general population (25). *Segmental vitiligo* has no such association with autoimmune thyroiditis, and is, in fact, *rarely associated with* any *autoimmune disease*.

A number of additional pathologies have also been linked to vitiligo. Loss of hair pigmentation has been associated with vitiligo (27). Subclinical ocular pathologies, especially uveitis and/or major fundal pigmentary abnormalities, are frequently encountered in children with nonsegmental vitiligo (28). Vogt-Koyanagi-Harada Syndrome is a disorder consisting of vitiligo as well as ocular and neurological abnormalities (28,29). It results from an autoimmune reaction against the ocular melanocytes of the uveal tract with variable extension to meningeal, cochlear and epidermal melanocytes.

Differential diagnosis

In children especially, there are many similarities in the clinical appearances of vitiligo, pityriasis alba, tinea versicolor, postinflammatory hypopigmentation, piebaldism, morphea, leprosy, tuberous sclerosis, nevus depigmentosus, and lichen sclerosis and atrophicus. To properly diagnose vitiligo, one must be able to differentiate between a complete absence of pigment, hypopigmentation and normal skin. This is more difficult in light-complexioned patients. Wood's lamp examination can help make this differentiation easier. One particularly difficult differentiation is between the macules of confetti vitiligo and those of tuberous sclerosis (30). Characteristic signs and symptoms may be helpful in making the proper diagnosis in this and other cases. For example, depigmented patches shaped like ash leaves would help make the diagnosis of tuberous sclerosis. In another situation, the presence of a white forelock may be helpful in diagnosing piebaldism as apposed to vitiligo.

Etiology

Nonsegmental vitiligo is most commonly described as having an autoimmune etiology. The immune system is undeniably involved in the pathogenesis, as evidenced by the effectiveness of immunomodulatory agents, such as corticosteroids and calcineurin inhibitors in treatment (31,32). Its strong association with autoimmune diseases further supports this hypothesis

Table 2. Vitiligo treatment.

	efficacy	comment
PUVA	51%[56]	High relapse rate[56]
NB-UVB	63%[56]	Treatment of choice for vitiligo vulgaris[56]
Targeted Phototherapy	53%[59]	Useful in treating focal vitiligo[48]
Skin Grafting	87-95%[56]	Treated of choice for stable lesions[56]
Corticosteroids	56%[56]	Primarily used in combination therapy[66-68]
Calcineurin- Inhibitors	25%[63]	Primarily used in combination therapy[66-68]
Calcipitriol	56%[64]	Primarily used in combination therapy[66-68]

(26,27). There are two immune system abnormalities observed in vitiligo patients that provide possible mechanisms for the melanocyte destruction that occurs. Several studies have detected the presence of autoantibodies in serum targeting melanocyte surface and cytoplasmic antigens (33). In vivo demonstration of melanocyte destruction by vitiligo patient IgG serum adds plausibility to this mechanism (34). Lately, a cell-mediated mechanism has been receiving more attention. Cytotoxic T-lymphocytes (CTL) have been spatially and temporally associated with depigmentation (35). A recent study reported especially dramatic inflammatory changes, including CTL influx, where one would expect to find the most active pathology: in lesional margins and in the center of newly formed lesions (36). Inflammatory infiltrates from vitiliginous lesions have been found to contain T-cells specific to melanocyte antigens (37). The credibility of this mechanism is further supported by studies demonstrating an autoimmune response against antigens present in normal melanosomes in patients with melanomas (38).

Other hypotheses revolve around melanocyte self-destruction. Some studies suggest that melanocyte defects that result in increased oxidant stress may explain melanocyte dysfunction (39,40). Increases in pro-oxidants as well as decreases in anti-oxidant agents have been reported in patients with vitiligo. Furthermore, several studies detected evidence of oxidative stress-induced damage within the epidermis of vitiliginous lesions (39). An alternative hypothesis, the melanocytorrhagy theory, suggests autologous melanocyte chronic detachment and transepidermal loss as a possible explanation (40). Disruption of the linkage between keratinocyte cytokines and their receptors (expressed on melanocytes) is another proposed etiology (41).

There are several other more limited hypotheses regarding vitiligo etiology. *Segmental vitiligo* is best explained by the neural theory, which proposes that some chemical mediators released from peripheral nerve endings cause decreased production of melanin (42). Recent studies have reported ultrastructural evidence of axonal damage (43) and changes in neuropeptide balance (44) in the nerves of segmental vitiliginous lesions, supporting this hypothesis. Some medications have been associated with vitiligo development. For example, infliximab has been described as inducing vitiligo, presumably by the same mechanism as it produces a lupus-like syndrome (45). A chemical-induced vitiligo can result from exposure to some industrial chemicals, catechols, alkylated phenols and cinnamic aldehyde (46,47). Trauma to the skin can cause focal depigmentation in patients with vitiligo (2). This occurrence, known as Koebner's phenomenon, is rarely seen in segmental vitiligo, but is seen in a third of patients with nonsegmental vitiligo. Psychological trauma may even increase an individual's susceptibility to vitiligo (48).

Histopathology

Histopathological examination of vitiligo lesions using melanocyte-specific stains has shown few melanocytes in early lesions and a lack of melanocytes in well-established lesions (27). In patches with hyperpigmented borders, the margins were found to contain enlarged melanocytes with elongated dendritic processes containing melanin. A lymphohistiocytic infiltrate along with focal basal layer vacuolar changes has been observed in marginal tissue. Significantly more infiltrate and other inflammatory changes were appreciated in marginal areas and early lesions in one study (36).

Repigmentation of vitiliginous lesions occurs predominantly in a perifollicular pattern (49). The outer root shaft of hair follicles contains an inactive melanocyte reservoir. Upon stimulation by certain treatment modalities, these melanocytes divide, proliferate and migrate into the adjacent tissue where they become activated. Repigmentation also may occur in diffuse, marginal or combined patterns depending on the particular methods of treatment used. These patterns probably effect repigmentation through mechanisms other than the one described for the perifollicular pattern.

Treatment

Topical psoralen plus UV-A phototherapy (PUVA therapy) is a well-established treatment for nonseg-

mental vitiligo (Table 2). However, it is only moderately effective (51%) and has a high relapse rate (50). It has been associated with a number of side-effects, including darkening of normal skin, erythema, scaling and pruritus. Less common side-effects include phototoxic effects, photoallergic reactions, hyperkeratosis of lesional skin, and, rarely, skin malignancies. Khellin is an extract of an Eastern Mediterranean plant that has a chemical structure similar to psoralen. A recent study has shown that treatment with UV-A and khellin in place of psoralen results in comparable efficacy (44% for KUVA vs. 53% for PUVA) with a large reduction in adverse effects (51).

Narrow-band UV-B (NB-UVB) phototherapy is a treatment of choice for patients with active, generalized vitiligo with an effectiveness of 63% against this form of the disease (50). It has also been shown to be highly effective in treating stable vitiligo when at least 5% of the total body is involved (52). Cosmetic results are better with this therapy compared to PUVA with decreased contrast between normal and lesional skin being reported. It is associated with far fewer side-effects, possibly due to a simpler treatment procedure resulting in shorter sessions and decreased ultraviolet exposure time (42).

Targeted phototherapy using the excimer laser is especially useful in treating localized vitiligo. The hyperpigmentation of normal skin reported with PUVA treatment is also not observed with this treatment. However, this modality has been found to be slightly less effective than NB-UVB with a success rate of 53% (53). Still, a number of characteristics of the treatment make it a valuable therapeutic option. The targeted exposure of this strategy spares the normal skin from potentially harmful radiation. Also rapid therapeutic responses have been observed in several studies (42), with one study observing a 52% success rate within 3 months (53). These two factors together result in a large decrease in the cumulative dosing, which may reduce adverse effects and increase patient compliance.

Surgical modalities are quite effective in treating certain types of vitiligo. Autologous skin grafting is a method of choice for treating stable vitiligo, focal or generalized. Segmental vitiligo, which is particularly unresponsive to medical treatment, can be managed well with this treatment. (3). The success rate is estimated to be between 87% and 95% (50). The procedure can be very complicated, having to be performed under general anesthesia. Additionally, it is only indicated for patients in whom the vitiligo has stopped progressing (54). Mini-grafting techniques have been utilized with some success to determine lesion stability (55). Another surgical treatment, manual tattooing of depigmented lesions, is a cheap and effective alternative for patients with any type of localized vitiligo (56).

Topical therapeutics are frequently used in the treatment of vitiligo. Melagenine, a topical agent derived from placenta, has been used successfully in treating some childhood cases of vitiligo (57). Corticosteroids have been shown to be moderately effective in monotherapy with a success rate of 56% (53). Possible side-effects, including atrophy and telangiectasias limit its use in some populations. More recently, the calcineurin-inhibitors pimecrolimus and tacrolimus have been used successfully in vitiligo treatment (44,58-60). However, patients have been reported to receive only mild benefit from exclusive calcineurin-inhibitor treatment, with a success rate of 25% after 2 months of therapy reported by one study (32, 58). Calcipotriol is another topical agent being utilized. It is thought to stimulate melanogenesis through an unknown mechanism involving melanocyte 1-alpha-25 dihydroxy vitamin D3 receptors. In one trial, 10/18 children (56%) treated showed marked to complete repigmentation (61). Because of their limited effectiveness in monotherapy, the above topical therapies are used primarily in combination therapy to increase the efficacy and, in some cases, decrease the response time of other modalities (59,62,63).

Extensive vitiligo, vitiligo universalis, may be treated with removal of pigment from the remaining normally pigmented skin. Bleaching creams used for this purpose include monobenzyl ether of hydroquinone and 4-methoxy-phenol. More recently, a Q-switched alexandrite was used to treat recalcitrant repigmentation in a woman with pervasive vitiligo, successfully and with minimal recurrence at 12-month follow-up (64).

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