Vitiligo

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Abstract

Vitiligo is an acquired skin disorder characterized by white and depigmented patches enlarging and becoming more numerous with time. It is due to a disappearance of functioning melanocytes and loss of melanin in the epidermis. The condition can be cosmetically disfiguring and the lesional skin is thus more sensitive to sunburns. It affects 0.1-2% of the world’s population, irrespective of gender and race. Etiology is unknown and the several pathogenetic hypotheses do not account for the entire spectrum of the disease. Although no full therapeutic solution for vitiligo is available, many options may lead to acceptable results in most patients. Management includes sun protection, as well as medical and surgical repigmentation therapy. Medical treatments consist of narrowband ultraviolet B (UVB), broadband UVB, psoralen plus UVA, corticosteroids and other novel approaches. Surgical treatment, consisting of autologous transplantation methods, is generally recommended for stable/focal vitiligo, after medical therapy has failed. Finally, for patients with extensive areas of vitiligo, depigmentation of the residual melanin should be taken into account.

Keywords: vitiligo, melanocytes, immune response, neural mediators, oxidative stress, epidermal microenvironment, repigmentation therapy.

Definition

Vitiligo is a non contagious acquired pigmentation disorder characterized by sharply-defined white patches of variable shape and dimensions, increasing in size and number with time. The histological picture shows loss of melanocytes and melanin in the white patches and an inconstant lympho-mononuclear infiltrate in the advancing margins of vitiligo (1).

Diagnostic criteria

Diagnostic criteria are based on the findings of acquired, well-demarcated white lesions on the skin, with no associated inflammation. These lesions tend to enlarge centrifugally.

Differential diagnosis

Differential diagnosis is made versus: 1) piebaldism, which is a rare depigmentation disorder due to a mutation of c-kit
protooncopgene affecting the differentiation and migration of melanocytes. It is characterized by stable and circumscribed white patches (with absence of melanocytes) present at birth, affecting the face (especially the central area with localized poliosis), sternal and abdominal zones, knees and elbows;

2) achromic nevus, which is a well-limited depigmented area, stable and evident at birth, in which melanocytes are either normal or reduced;

3) post-inflammatory leukoderma (e.g., after psoriasis or syphilis) in which patients have a history of pre-existing dermatosis;

4) pytiriasis versicolor, where mycologic examination reveals hyphae and spores;

5) depigmented lesions in leprosy, which shows anesthetic disturbance of sensibility.

Frequency
Vitiligo is the most common pigmentary disorder affecting 0.1-2% of the world’s population, irrespective of race and gender (2).

Clinical description
The clinical picture consists of one or more well-demarcated and white macules, progressing in size and number. They are asymptomatic generally. The lesions usually appear on sun-exposed or constitutionally hyperpigmented areas or on sites of stretch and pressure (face, dorsum of hands and fingers, external genitalia, knees and elbows). The margins of the patches are often hyperpigmented; hypopigmented areas sometimes occur together with the depigmented lesions and the normally pigmented skin (trichrome vitiligo). Rarely an inflammatory border may be found around the vitiligo patch resulting in a raised and erythematous edge (inflammatory vitiligo). Poliosis circumscripta, as well as canities and premature graying, can be observed; mucosae are rarely involved.

Vitiligo classification by Nordlund
Nordlund established a clinical classification based on distribution and extension of lesions (3). Three types have been delineated: localized, generalized and universal vitiligo.

Localized vitiligo
Localized vitiligo is classified into focalis (one or more patches in one area but not in a segmental pattern) and segmental (one or more maculae in dermatomal distribution) forms.

Generalized vitiligo
Generalized vitiligo can be subdivided into acrofacial (affecting face and distal extremities), vulgaris (the most common variety, with a symmetrical distribution of lesions in typical zones) and mixed (segmental plus vulgaris or acrofacial) types.

Universal vitiligo
Universal vitiligo involves more than 80% of the body.

Vitiligo classification by Koga
This is a more recent classification subdividing vitiligo into two clinical types: vitiligo non segmentalis (type A) and vitiligo segmentalis (type B) and (4).

Type A
Type A is more common, has a potential lifelong evolution and is associated with Koebner phenomenon and frequently with autoimmune diseases, such as Sutton nevus, thyroid disorders, juvenile diabetes mellitus, pernicious anemia and Addison’s disease.

Type B
Type B is rarer and has a dermatomal distribution; after rapid onset and evolution it usually exhibits a stable course.

The natural course of the disease is generally unpredictable, but it is often progressive; some degree of spontaneous repigmentation occurs in 10-20% of patients, but it is rarely cosmetically acceptable (5), often occurring in a perifollicular pattern.

Management and treatment
Treatment of vitiligo includes cosmetic camouflage for the lesions on sun-exposed skin and mandatory prescription of sunscreens in sunny climates.

Medical and surgical repigmentation therapies can be carried out (6).

Medical treatments
Photochemotherapy
It consists of photosensitizing psoralen plus ultraviolet A (PUVA) or natural UV (PUVASOL). Efficacy has been noted in a proportion of cases. In systemic treatment, 8-methoxypsoralen or 5-methoxypsoralen or 4,5,8-trimethylpsoralen is administered per os 2h before radiation exposure. The UV dosage is gradually increased until minimal erythema of vitiligo lesions occurs. Patients go through this treatment twice a week for at least 6 months. UV blocking sunglasses should be used. Topical applications of psoralen may be hazardous and can result in skin blistering. However, phototoxic reactions, pruritus and xerosis may represent the short-term cutaneous adverse effects of PUVA, while skin disorders (such as lichenification, actinic elastosis, actinic keratosis and cutaneous malignancies) may be the long-term cutaneous adverse reactions. Oral PUVA may induce short-term systemic adverse effects, such as nausea, gastric disturbance, headaches, elevation in liver function tests. Cataract has also been described as related to oral PUVA (7). Contraindications for PUVA therapy are skin type I (i.e. skin that will never tan and always burn), skin malignancies, pregnant or lactating women and children aged

less than 12 years. PUVA therapy seems to act via stimulation of melanocytes of hair follicles or of the edge of achromic lesions, and possibly through a suppression of immunological activity.

**Broadband UVB**

This phototherapy uses an emission spectrum of 290 to 320 nm (8). Caution is needed during the UVB dose increments. Patients are treated twice to three times a week for long periods. Short-term cutaneous adverse effects include pruritus, erythema, xerosis. The mechanism of action is unknown.

**Narrowband UVB**

In this phototherapy an emission spectrum of 310 to 315 nm is used (9). The UV dose is gradually increased until reaching minimal erythema of white lesions. Treatment is administered twice a week. The advantages of this therapy over PUVA regimen are represented by shorter time of treatment, less side effects, no oral drug administration, no contraindications in children or lactating women. Narrowband UVB leads to erythematous reactions less frequently than broadband UVB.

**Corticosteroids**

Corticosteroids can be used topically and orally. Generally low or mid potency preparations are utilized. Creams are applied once or twice per day in localized lesions, carefully trying to avoid local adverse effects. The mechanism of action is still unclear, possibly due to a suppression of inflammation.

**Surgical treatments**

They consist in autologous transplantation methods, indicated generally in vitiligo patients unresponsive to medical therapy and with stable (commonly segmental) vitiligo (6). These treatments include the use of minigrafting. A 2-mm full thickness punch graft is collected from normally pigmented sites and transplanted onto a depigmented area where similar punched out skin has been extracted, or of thin split-thickness skin grafting obtained from a normally pigmented site and transplanted onto a dermabraded depigmented area; later the grafted area is irradiated with UVA. Scarring at the donor site and infections at the recipient site are possible. Another approach uses the roof of a suction blister produced in normally pigmented skin to cover the denuded areas obtained in lesional skin where a blister formation has been induced and the depigmented epidermis has been removed; in this case no scarring occurs at the donor site. Transplantation onto a previously denuded achromic area can be done also with cultured autologous melanocytes, using either melanocytes or melanocytes mixed with keratinocytes; such techniques require specialized laboratories and are expensive.

Depigmentation therapies should be considered for patients with more than 80% of skin affected by vitiligo. These patients should be informed that depigmentation of residual melanin is a permanent process, so that after therapy they will be at lifelong risk of sunburns. The substance commonly used is topic monobenzylether of hydroquinone, a potent melanocytotoxic agent capable of inducing depigmentation at distant sites also (10). Adverse effects include contact dermatitis and acquired ochronosis.

**Novel therapies**

**Microphototherapy**

In this approach, a narrowband UVB is focused only onto the depigmented skin, so that unaffected skin areas are not exposed to UV irradiation. This therapy requires expensive equipment and trained personnel (11).

**Pseudocatalase plus UVB therapy**

Based on the evidence of epidermal H2O2 accumulation and reduced catalase activity in vitiligo, this treatment uses a narrow band UVB-activated pseudocatalase complex in combination with calcium, which is applied topically and seems to be able to remove epidermal H2O2 in association with a recovery of functioning melanocytes (12); a worldwide open clinical trial is currently underway.

**Systemic antioxidant therapy**

Based on the demonstration of an abnormal oxidative stress in vitiligo epidermis (13), the oral administration of antioxidant agents such as selenium, tocopherol, methionine and others, is given for long periods.

**Etiology and pathogenesis**

Etiology is still unknown, but some evidence-based pathogenetic hypotheses have been proposed to explain the loss of melanocytes in epidermis.

**Genetic hypothesis**

A positive family history for vitiligo is reported. Actually, family clustering of cases is not uncommon, since about 20% of patients have at least one affected first-degree relative, with a non-Mendelian pattern suggestive of multifactorial, polygenic inheritance (14); segregation analyses suggest the involvement of multiple interacting genes in different populations (15). Several genes and chromosomal regions have been implicated in susceptibility to vitiligo, but none has been confirmed so far (16). In addition, several HLA abnormalities have been associated with vitiligo, including association with Dr4, B13, BW35, and A30 (17). A very recent and large epidemiological study supports the involvement of both genetic and non genetic factors in the pathogenesis of the disease and

http://www.orpha.net/data/patho/GB/uk-vitiligo.pdf
suggests that some genetic factors may be shared with other autoimmune diseases (16).

**Autoimmune hypothesis**

This hypothesis proposes that an immune system disorder results in destruction of melanocytes. It is first supported by the frequent observation that several autoimmune disorders (thyroid diseases, Sutton nevi, juvenile diabetes mellitus, porcine anemia and Addison’s disease) are associated with vitiligo. A significant association of vitiligo was demonstrated with thyroid dysfunction and/or thyroid antibodies in particular (18).

Concerning humoral immunity, antibodies to surface and cytoplasmic antigens of melanocytes have been found in vitiligo patients, mainly belonging to the IgG class. The autoantigens most frequently identified are antigens related to HLA class I molecules, tyrosinase, tyrosinase-related protein (TRP)-1 and TRP-2 (the last three are melanocyte-specific antigens) (19). However, the pathogenetic role of antimelanocyte antibodies remains unclear. The serum levels of antibodies to melanocyte antigens seem to correlate with activity and extent of the disease and with the presence of other immune disorders, and to decrease in vitiligo patients responding to therapy (19).

It is likely that both humoral and cellular immunity co-operate in the destruction of melanocytes.

Concerning cellular immunity, an important role has been given to the infiltrate underlying the pigmented lesional skin, where CD4 and CD8 positive T cells were detected, also expressing activation molecules (20). A substantial number of infiltrating T cells express the cutaneous lymphocyte antigen (CLA) typical of skin homing T cells (20), and a recent study localized CLA positive cytotoxic T cells in apposition to disappearing melanocytes in the perilesional skin (21). In vitiligo patients, high frequencies of Melan-A/Mart1 (a melanosomal antigen) specific CD8 positive T cells were detected in peripheral blood (1). Interestingly, Melan-A/Mart1 specific CD8 positive T lymphocytes were identified in inflammatory lesions of melanocyte destruction following infusion of Melan-A/Mart1 specific CD8 positive T-cell clones in melanoma patients (22); this finding gives direct evidence of T-cell-mediated vitiligo.

**Neural hypothesis**

This hypothesis suggests that some neurochemical mediators, possibly secreted from contiguous nerve endings, are cytotoxic for pigment cells. This theory is supported by the existence of segmental variant of vitiligo that affects a dermatome, by the occurrence of vitiligo after a period of severe emotional stress, and by the onset of disease in patients with neurological disorders or with peripheral nerve injury (23, 24). Abnormalities of neuropeptides have been observed in perilesional skin and in blood of vitiligo patients (25). In addition, increased catecholamine discharge or synthesis has been associated with disease activity, suggesting a role of catecholamines in the depigmentation process (26). Important support to this theory has been given by the demonstration of morphological and functional communication between epidermal melanocytes and nervous system (27).

**Autocytotoxic/metabolic hypothesis**

Oxidative stress has been suggested to be the initial pathogenetic event in melanocyte degeneration (28, 29) with H2O2 accumulation in the epidermis of patients with active disease (12). Defective recycling of tetrahydrobiopterin has been reported in vitiligo epidermis, associated to the intracellular production of H2O2 (28, 12). In addition, an alteration in the antioxidant pattern, with a significant reduction of catalase activity, has been demonstrated in both lesional and non lesional epidermis of patients (30), as well as in melanocytes (29). However, the antioxidant imbalance has been confirmed also in peripheral blood mononuclear cells of active vitiligo patients; it was correlated to an increased intracellular production of reactive oxygen species and appeared to be due to a mitochondrial impairment (31). These findings support the concept of a possible systemic oxidative stress in vitiligo.

**Novel microenvironment-related hypothesis**

Cytokine imbalance in the epidermal microenvironment has been demonstrated in lesional skin in active vitiligo. This could impair normal life and activity of melanocytes; a decrease in cytokines stimulating melanocytes and an increase in cytokines inhibiting melanocytes (in particular, tumor necrosis factor-α) were detected in depigmented lesions (32). According to this hypothesis, a central role is assigned to cutaneous microenvironment.

**Convergence theory**

The description of many credible contributory factors to the pathogenesis of vitiligo led to this theory, in which different causal elements may act synergistically or independently to provoke disappearance of melanocytes. Genetic factors, oxidative stress, autoimmunity, mutations, altered cellular environment can all contribute to the disease (33).

**Diagnostic methods**

The diagnosis is mainly based on clinical evaluation. Evolution of the disease allows differential diagnosis versus piebaldism and achromic nevus; mycological examination is
Important to exclude pythiadias versicolor. Accurate occupational history is useful to exclude possible exposure to bleaching agents.

Unresolved questions
The cause of vitiligo remains unknown, and it is still unclear whether the abnormalities described in the single pathogenetic theories are a cause or rather an effect of the disease. This fact is reflected over the lack of a definitive effective therapy.

References