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Vitiligo as an Autoimmune Disease

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Abstract

Background: Vitiligo is an acquired cutaneous disorder characterised by depigmented patches on the skin and mucous membranes, due to the loss of functioning melanocytes. Vitiligo is a multifactorial polygenic disorder with a complex pathogenesis. Although several theories have been proposed about the pathogenesis of vitiligo, the precise cause remains unknown. Theories regarding destruction of melanocytes include autoimmune mechanisms, cytotoxic mechanisms, an intrinsic defect of melanocytes, oxidant-antioxidant mechanisms, and neural mechanisms. Autoimmune hypothesis is based on the clinical association of vitiligo with certain diseases known as autoimmune. The autoimmune theory proposes alteration in humoral and cellular immunity in the destruction of melanocytes.This article presents you a recent overview of autoimmune basis of vitiligo.

Introduction

Vitiligo is an acquired disorder of pigmentation characterized by the loss of melanocytes from the epidermis. Vitiligo occurs worldwide, with a prevalence of 0.1-2.0 %, with the disease beginning before the age of 20 in 50% of cases. It 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.

In vitiligo there is a marked absence of melanocytes and melanin in the epidermis. Electron microscopic studies confirm the loss of melanocytes, which appear to be replaced by Langerhans' cells.

Clinically hypomelanotic macules are usually first noted on the sun-exposed areas of skin, on the face or on the dorsa of hands. The lesions are usually well-demarcated, but the margins may be scalloped. Lesions enlarge centrifugally at an unpredictable rate and can appear on any body sites, including mucous membranes. Vitiligo is classified as segmental, acrofacial, generalized and universal or by pattern of involvement as focal, mixed, and mucosal types [**1, 2, 3**].

Currently, the exact aetiology of vitiligo remains obscure, but many factors have been implicated in the development of the disease including infectious, stres, neural abnormalities, melatonin receptor dysfunction, impaired melanocyte migration and genetic susceptibility. There are three hypotheses that explain the pathogenesis of vitiligo. They all try to confront the reason of melanocytes destruction. These are the neural hypothesis, self destruction hypothesis and autoimmune hypothesis. Different pathogenic mechanisms could account for the various clinical types of vitiligo: the neural theory is usually related to segmental vitiligo whereas the autoimmune

theory is thought to be involved in the generalized (non segmental) form of the disorder.

Neural hypothesis: vitiligo lesions often follow a dermatomal pattern, so it has been suggested that a neurochemical mediator is responsible for destroying the melanocytes. The neural hypothesis is thought to be involved in segmental vitiligo. Although electron microscopy shows abnormalities of terminal portions of peripheral nerves, there is little support for this hypothesis. There are also changes in neuropeptid levels in the affected area; VIP, Neuropeptid Y and Calcitonine related gene protein is found higher in the depigmented macules [**4, 5, 6**].

Self-destruction hypothesis: This suggests that melanocytes destroy themselves due to a defect in a natural protective mechanism that removes toxic melanin precursors. In vitiligo patients epidermal H2O2 levels are found increased and catalase levels are decreased [**5**].

Autoimmune Hypothesis

Vitiligo is often associated with other autoimmune diseases (**Table 1**). The association with autoimmune disorders and organ specific antibodies as well as the fact that non-surgical repigmenting therapies have immune-modulating effects indirectly support the idea of an autoimmune pathogenesis of the disease.

In vitiligo patients, elevated frequencies of autoimmune thyroid disease, *Addison*'s disease, systemic lupus erythematosus and pernicious anemia were found [**3, 6**]. In recent studies on larger patient groups, a significant association of vitiligo was demonstrated with thyroid dysfunction and/or thyroid antibodies. Associated thyroid dysfunction may be at the subclinical or the clinical level and is diagnosed as *Graves*' disease, *Hashimoto*'s thyroiditis, hyperthyroidism or hypothyroidism. Vitiligo often precedes thyroid disease indicating a need for regular screening for dysfunctional thyroid antibodies. The frequency of organ spesific autoantibodies (parietal, adrenal, thyroid antibodies) varies and often exceeds the frequency of overt clinical organ-specific autoimmune disease. The presence of organ-specific antibodies or an associated disease seems to correlate with the duration of vitiligo but not with the clinical features of the disease. Organ-specific antibodies are rather considered as a positive marker for subsequent development of clinical or subclinical autoimmune disease, justifying a regular functional investigation of the target organs during patient follow-up. Antibodies against melanocytes' surface antigens are provided evidence that the extent of depigmentation correlates well with the incidence and level of antibodies against melanocytes. Anti-tyrosinase antibodies, antimelanin antibodies and antikeratinocyte antibodies are other remarkable antibodies that can be demonstrated in vitiligo patients. Anti-tyrosinase antibodies can be seen in both generalized and localized vitiligo. Its levels are higher in the active, spreading phase of the disease [**6, 7, 8**].

Humoral Immunity

Several circulating autoantibodies have been found in sera of vitiligo patients. A few of them are specific for pigment cells. However it is stil unknown how an apparently selective destruction of melanocytes occurs in vitiligo. Melanocytes might be much more sensitive to toxic or immune-mediated injury than other cutaneous cell types. A few specific autoantigens are identified. VIT 40 seemed to be related to HLA class I molecules. Tyrosinase and tyrosinase related proteins 1 and 2 (TRP1 and 2) are key enzymes involved in melanin synthesis primarily localized to melanosomes and have been recently implicated as autoantigens. TRP1 was found to be expressed on the surface of melanocytes. Anti-TRP 2 levels were also reported in a high percentage of vitiligo patients. Also the melanosomal matrix protein gp 100 has been reported as an humoral autoantigen in only 5% of vitiligo patients.

Recently the surface receptor, melanin concentrating hormone receptor 1 (MCHR 1) was detected as an autoantibody target in 16% of vitiligo patients. How antibodies to pigment cells arise in vitiligo patients has not been elucidated. They might result from a genetic predisposition to immune dysregulation at the T or B cell level. An immune response to damaged pigment cells might also result in the presence of antimelanocyte autoantibodies that might further aggrevate melanocyte loss [**3, 6, 9, 10**].

Table 1. Vitiligo Associated Autoimmune Diseases

Thyroid disease
Diabetes mellitus
Adrenal insuffiency
Lupus erythematosus
Alopecia areata
Myasthenia gravis
Pernicious anemia
Rheumatoid arthritis
Sarcoidosis
Vogt-Kayanagi-Harada syndrome
Multipl autoimmune disease
Psoriasis
Lichen planus
Chronic active hepatitis

Cellular Immunity

T cell infiltration in the margin of inflammatory vitiligo is detected as a participation of cellular immunity in pathogenesis of vitiligo. Immunohistochemical studies of the perilesional area in generalized vitiligo mainly detect CD4 and CD8 positive T cells in the infiltrate which express activation molecules such as IL-2 receptor, HLA-DR and MHC 3 complex. The dermal and epidermal infiltrates consist of cytotoxic and helper T cells that are closely associated with the areas of melanocyte depletion. Also decreased CD4/CD8 ratio was found [**3, 6, 7, 11**]. In one study, $CD8^+$ T lymphocyte reactivity to the melanocyte antigen gp100 and to a lesser extent MelanA/MART-1 was detected. The disease activitiy is found to appear to correlate with reactivity to gp100 [**12**]. Macrophage infiltration has been demonstrated in vitiligo lesions with increased numbers present in perilesional skin. Langerhans' cells present antigen to the T cells in the epidermis. The Langerhans' cells in vitiligo patiens may be found normal, increased and decreased compared with pigmented skin from the same patients and from control subjects. The increase of its number may contribute the melonocyte destruction in immunological way in vitiligo skin [**3, 5, 6, 7**].

Serum IL-2R levels can be used to monitor in vivo immune activation, and its elevation has been correlated with T cell mediated immun disease. Soluble IL-2R increased levels are seen especially in generalized, focal and non-dermatomal types of vitiligo. Also tissue fluids from the margin of hypopigmented macules, especially in active disease, seem to contain higher levels of sIL-2R than uninvolved skin of the same patient. The production of IL-6, IL-8 by monocytes is increased in vitiligo patients. The cytotoxic T lymphocyte antigen-4 (CTLA-4) gene product is involved in the negative regulation of T cell activation and in controlling T cell apoptosis. Several CTLA-4 polymorphic alleles are associated with susceptibility to autoimmune disease and some of these have now been associated with vitiligo, suggesting that the skin depigmenting disease may have an autoimmune aetiology. But CTLA-4 polymorphic markers are only seen in vitiligo patients that associated with other autoimmune diseases. Recent research focuses on a melanocyte-spesific cytotoxic T cell immune reaction in the destruction of melanocytes. Circulating melanocyte spesific cytotoxic T cells have been detected in high frequencies in vitiligo patients [**3, 6, 7**].

In recent studies, BAFF (B lymphocyte activating factor) a new ligand of the TNF cytokine family, is shown that overexpression of it may cause a breakdown of self-tolerance and subsequently cause autoimmune vitiligo via several possible mechanisms. BAFF may activate the B cells to produce autoantibodies in vitiligo, BAFF-activated B cells promote the activitiy of self-reactive CD4+ T cells in vitiligo, BAFF-activated B cells promote the activitiy of self reactive CD8+ T cells in vitiligo, BAFF directly regulates T cell activation leading to self tolerance breakdown in vitiligo or autoimmune regulator defiency may result in BAFF overexpression in vitiligo [**13**].

Animal Models

Autoimmune vitiligo is studied in Smyth chickens. They express a genetically inherited form of vitiligo-like depigmentation resulting from the loss of melanocytes in feather and ocular tissues. Recent data suggest that the mechanism involved in the death of melanocytes in Smyth line vitiligo is an apoptosis induced by infiltrating cytotoxic T lymphocytes. Autoantibodies to chicken melanocytes have also been detected in the sera of 100% of Smyth chickens. These antibodies were found both before and during the presentation of vitiligo. They also have a decreased CD4/CD8+ ratio during the process of leukoderma. Immunosupressive treatment or bursectomy have been shown to reduce depigmentation. In other animals with vitiligo

including horses, cats, and dogs, antipigment cell antibodies that recognise a similar pattern of melanocyte antigens to humans have been detected. Although each animal model helps in the study of different facets of melanocyte destruction, until a spesific marker of vitiligo is demonstrated, none of them can be considered a precise model [**3, 7, 9, 14**].

The pathogenesis of vitiligo remains complex and partially understood. Autoimmunity seems to play a significant role in its causation in a considerable number of patients. It is highly probable that the several clinical phenotypes of vitiligo are underlined by different physiopathological mechanisms. However further studies on the local immune reaction in vitiligo skin are needed to reveal the pathway of melanocyte destruction [**6, 9, 15**].

References

1. Halder RM, Taliaferro SJ. Vitiligo. In: Fitzpatrick's Dermatology in General Medicine. Volume 2. Eds. Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ. 7th Edition. New York, Mc Graw-Hill, 2008; 616-622.
2. Bleehen SS, Anstey AV. Disorders of the skin colour. In: Rook's Textbook of Dermatology Volume 2. Eds. Burns T, Breathnach S, Cox N, Griffiths C. 7th Edition. Massachusetts, Blackwell Publishing, 2004; 39.1-39.68.
3. Rezaei N, Gavalas NG, Weetman AP, Kemp EH. Autoimmunity as an aetiological factor in vitiligo. J Eur Acad Dermatol Venereol 2007; 21: 865-876. PMID:17658994
4. Ramrath K, Stolz W. Disorders of Melanin Pigmentation. In: Braun-Falco's Dermatology, Eds. Burgdorf WHC, Plewig G, Wolff HH, Landthaler M. 3rd Edition. Heidelberg, Springer verlag; 2009; 957-982.
5. Özpoyraz M, Acar MA. Pigmentasyon Bozuklukları. In: Dermatoloji. Eds. Tüzün Y, Gürer MA, Serdaroğlu S, Oğuz O, Aksungur VL. 3rd Edition. İstanbul, Nobel Tıp Kitabevleri, 2008; 1445-1528.
6. Ongenae K, Van Geel N, Naeyaert JM. Evidence for an autoimmune pathogenesis of vitiligo. Pigment Cell Res 2003; 16: 90-100 PMID: 12622785
7. Sehgal VN, Strivastava G. Vitiligo: Autoimmunity and immune responses. Int J Dermatol 2006; 45: 583-590. PMID: 16700798
8. Tanioka M, Yamamoto Y, Katoh M, Takahashi K, Miyachi Y. Vitiligo vulgaris and autoimmune diseases in Japan. Dermatoendocrinol 2009; 1: 43-45. PMID: 20046588
9. Passeron T, Ortonne JP. Physiopathology and genetics of vitiligo. J Autoimmun 2005; 25: 63-68. PMID: 16298511
10. Kemp EH, Gavalas NG, Gawkrodger DJ, Weetman AP. Autoantibody responses to melanocytes in the depigmenting skin disease vitiligo. Autoimmun Rev 2007; 6: 138-142. PMID: 17289548
11. Spritz RA. The genetics of generalized vitiligo and associated autoimmune diseases. Pigment Cell Res 2007; 20: 271-278. PMID: 17630960
12. Mandelcorn-Monson RL, Shear NH, Yau E, Sambhara S, Barber BH, Spaner D, DeBenedette MA. Cytotoxic T Lymphocyte reactivity to gp100, MelanA/MART-1 and Tyrosinase, in HLA-A2-positive vitiligo patients. J Invest Dermatol 2003; 121: 550-556. PMID: 12925214
13. Lin X, Tian H, Meng X. Possible roles of B lymphocyte activating factor of the tumour necrosis factor family in vitiligo autoimmunity. Med Hypotheses 2011: 76; 339-342. PMID: 21075543
14. Ortonne JP. Vitiligo and other disorders of hypopigmentation. In: Dermatology. Volume 1. Eds. Bolognia JL, Jorizzo JL, Rapini RP. 1st Edition. Spain. Mosby, 2003; 947-973.
15. Boissy RE, Spritz RA. Frontiers and controversies in the pathobiology of vitiligo: separating the wheat from the chaff. Exp Dermatol 2009; 18: 583-585. PMID: 19320739