A Review of Pathogenesis, Genetic Polymorphisms, Diagnosis and Treatment Approaches of Vitiligo

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KEYWORDS

Vitiligo, cytokines, and genetic polymorphism

ABSTRACT

Vitiligo is a depigmenting skin condition characterized by a specific melanocyte depletion, resulting in melanin attenuation inside the skin's damaged regions. A distinguishing feature is a completely amelanotic, non-scaly, chalky-white macule with clear borders. The understanding of the etiology of vitiligo has advanced significantly in recent years. It is now categorically recognized as an autoimmune disorder associated with metabolism and oxidative stress, including cellular detaching diseases, as well as hereditary and environmental factors. The consequences of vitiligo can be mentally distressing and frequently have a significant impact on daily life; thus, this should never be dismissed as an esthetic or minor illness. The two main types of the condition recognized by a global consensus in 2011 were nonsegmental vitiligo (NSV) and segmental vitiligo (SV). The term "vitiligo" was chosen to refer to all NSV types (including acrofacial, mucosal, generalized, universal, mixed, and rare variants). One of the most important critical decisions made by this consensus was to distinguish SV from other types of vitiligo, especially given the implications for prognosis.

Introduction

Vitiligo is a depigmenting skin condition characterized by a specific melanocyte depletion, resulting in melanin attenuation inside the skin's damaged regions. A distinguishing feature is a completely amelanotic, non-scaly, chalky-white macule with clear borders (Gauthier et al ., 2003) . The understanding of the etiology of vitiligo has advanced significantly in recent years. It is now categorically recognized as an autoimmune disorder associated with metabolism and oxidative stress, including cellular detaching diseases, as well as hereditary and environmental factors factors (Gauthier et al ., 2003) (Krüger et al ., 2012). The consequences of vitiligo can be mentally distressing and frequently have a significant impact on daily life; thus, this should never be dismissed as an esthetic or minor illness (Krüger et al ., 2012). The two main types of the condition recognized by a global consensus in 2011 were nonsegmental vitiligo (NSV) and segmental vitiligo (SV). The term "vitiligo" was chosen to refer to all NSV types (including acrofacial, mucosal, generalized, universal, mixed, and rare variants). One of the most important critical decisions made by this consensus was to distinguish SV from other types of vitiligo, especially given the implications for prognosis (Krüger et al ., 2012) .Vitiligo is still a common and identifiable condition among dermatologists, most doctors, and several wise members of the general population. The disease's defining feature is hypopigmented patches, which are frequently first noticed on the fingertips, knuckles, and area surrounding

the lips, eyes, toes, and reproductive organs (van den Boorn et al ., 2009). The two most common ways for the skin to turn white are as follows. Melanocytes produce melanin and then pack them into melanosomes that are transferred to the surrounding keratinocytes through their dendritic processes, which are then injected into neighboring keratinocytes. Keratinocytes transport melanins and melanosomes through the epidermis's basal layer to the stratum corneum, where cells are desquamated and released into the surrounding environment (Rodrigues et al .,2017).

Types of vitiligo

The classification proposed by Taieb and Picardo (2010) was used as a working template for the Vitiligo Global Issues Consensus Conference (VGICC) revision of nomenclature (Table 1) (Taieb et al .,2010).

Types of vitiligo and their subtypes (Table 1)

Type of vitiligo	**Subtypes**
Non-segmental (NSV)	(Focal)[a], mucosal, acrofacial, generalized, universal
Segmental (SV)	Focal[b], mucosal, unisegmental, bi- or multisegmental
Mixed (NSV+SV)	According to severity of SV
Unclassified	Focal at onset, multifocal asymmetrical non-segmental, mucosal (one site)

Pathogenesis

The etio-pathogenesis of "generalized" or non-segmental vitiligo is better explained by autoimmune mechanisms as vitiligo often has autoimmune comorbidities and it often responds to immunosuppressive treatments (Lepe et al .,2003) .The reaction of immunity are cell-mediated, humoral (antibody-mediated), or through the cytokines.

The role of humoral immunity:

In 80% of active vitiligo patients, immunoglobulin G (IgG) and immunoglobulin M (IgM) against melanocytes were found. Low levels IgA also found in the inactive and control groups (Harning et al .,1991).Furthermore, anti-thyroglobulin antibodies, anti-thyroid antibodies, anti-thyroperoxidase, and antismooth muscle antibody are present. Those are typically related to thyroid disease and other autoimmune diseases (Ingordo et al .,2011) (Uncu et al ., 2011).

The role of cell-mediated immunity: Immunohisto-chemical examination of the inflammatory infiltrates in perilesional vitiligo skin using single and double immunostaining for melanocytes, Langerhans cells, T-cells, and macrophages revealed higher densities of melanocytes in normal skin, *vs* non-affected skin in subjects with vitiligo. These T cell had dramatic production of (IL-2R), and increased CD8:CD4 ratio. Thus, melanocytes destruction may be cytotoxic CD8 T-cell mediated. Perilesional HLA-DR production (MHC class II receptor) exhibited in all of the patients with vitiligo, especially along suprabasal and basal keratinocytes, due to local T cell reactivity. In addition, macrophages were numerous in vitiligo *vs* controls, whereas the CD36 subset of macrophages were higher in the later (Le Poole et al., 1996).

The role of cytokines in vitiligo

Cytokines are small, non-structural proteins or glycoproteins with molecular weights of less than 30 kDa (about 200 amino acids). They are secreted by cells in the immune system. Leukocytes, which are one type of cell that express cytokines and are responsible for regulating immunity, inflammation, and hematopoiesis, are an example of a cell that can do so. Over 200 different cytokines have been discovered up to this point

(Abdelbaseer et al., 2023). Cytokines have different immune activities. They combined to receptors of target cells and enhances a signal transduction (Elsaied et al. 2024) .There are significantly increased expression of tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), and IL-10 (Grimes et al., 2004) . As IFN-γ and TNF-α are T helper cell-1 cytokines, so vitiligo is mediated by the Th1 response (Taher et al ., 2009) . IL-17 plays role with macrophages, keratinocytes, and fibroblasts. In addition, it activates the expression of others, as IL-1 and IL-6, and TNF-α . Examination of sera and tissue of 30 vitiliginous subjects and 20 normal subjects showed significant higher levels of IL-17 toward vitiliginous subjects and disease duration (Bassiouny et al ., 2011) (Kolls et al ., 2004).

Viral theory

There is a strong association between vitiligo and chronic hepatitis C virus infection and autoimmune hepatitis (Akbayir et al ., 2004) . The sero-prevalence of HCV in individuals with vitiligo is not different from that of a control group, suggesting that HCV infection may not play a role in the pathophysiology of those patients (Abdel-Monem & Ali, 2024). In 2006 reported a low hepatitis B virus (HBV) sero-positivity in vitiliginous patients. Previous or concurrent cytomegalovirus (CMV) infections may induce the etio-pathogenesis or deterioration of vitiligo (Akcan et al ., 2006). Other viruses as Epstein-Barr virus, hepatitis E virus, herpes virus and the human immunodeficiency virus also have suspicious association with vitiligo (Toker et al ., 2007).

Intrinsic theory

Melanocytes in vitiligo have an intrinsic defect leading to their death. They demonstrate different abnormalities, including abnormal rough endoplasmic reticulum or deficiency of unidentified melanocyte growth factors such as basic fibroblast growth factor (bFGF) and decrease in the number of melanocytes expressing the c-kit receptor in lesional skin (Boissy et al ., 1991) (Norris et al ., 2009).

Integrated theory

Despite all the mentioned theories are attractive, it is likely that vitiligo is a result of the convergence of these pathological pathways. Most experts agree that vitiligo may be a syndrome with a multi-factorial etiology rather than a single entity (Halder et al .,2009).

Gene Polymorphisms and Vitiligo

Single-nucleotide polymorphisms (SNPs) of genes refer to the substitution of a single nucleotide at a specific position in the genome and account for most human heritable variations. There is convincing evidence that proinflammatory cytokines play a vital role in the initiation of vitiligo lesions (Sushama et al .,2019).

Human beta-defensin 1 (HBD-1)

Considering autoimmunity, HBD-1 and its gene polymorphisms have been evaluated in psoriasis (PSO), type 1 diabetes (T1D), oral lichen planus (OLP), inflammatory bowel disease (IBD), and systemic lupus erythematosus with variable degrees of association identified (Polesello et al .,2017) (Ozlu et al ., 2017). However the association between this gene polymorphism and vitiligo has not been studied enough in different populations (Ozlu et al ., 2017).

Interleukin-23 Gene

The IL-23R gene is located on chromosome 1p31. It is highly expressed in dendritic cells, and is involved in several chronic inflammatory diseases. The interleukin- 23 receptor (IL-23R) is composed of IL-23R and IL- 12Rβ1 subunits, which is shared with IL-12R (Parham et al., 2002) . IL-23/IL-23R is essential for the T-helper 17 (Th17) cell-mediated immune response. IL-23R plays an important role in the initiating, maintaining and accelerating the IL-23/IL-17 inflammatory signal transduction pathway (Zhang et al .,2014

) .Since then, IL23Rgene was proved to be the predisposing gene to many other autoimmune /inflammatory diseases. Certain SNP alleles in the IL-23R gene can up-regulate its expression on several immune cells, and amplify the inflammatory condition (Duvallet et al ., 2011).

Interleukin-6 (IL6) gene

IL6 is a pleiotropic cytokine, produced by macrophages, T cells and B cells, was initially designated as a B cell stimulator that promoted maturity of B-cells and the expression of immunoglobulins (Xu et al., 2017). During inflammatory conditions and infections, certain bacterial LPSs, interleukin-1b and tumor necrosis factor , are important stimuli for *IL6* production. (Zailaie et al ., 2005). Through different signaling pathways, *IL6* induces acute phase protein generation, contributing to the development of multiple inflammatory and autoimmune diseases (Ascoli et al ., 2019) .As a common clinical inflammatory factor, *IL6* has been shown to be significantly elevated in the body fluids of patients with vitiligo (Farhan et al ., 2014).

Tumor necrosis factor alpha (TNF-α)

Tumor necrosis factor-alpha (TNF-α) is a proinflammatory cytokine integral to the inflammatory response. Produced primarily by macrophage (El-Amir et al., 2025) .It also mediates inhibition of melanocyte stem cell differentiation as well as inhibition of melanin synthesis by deterring the enzymatic activities of tyrosinase and tyrosinase- related protein in melanogenesis. Therefore, TNF-α plays an important role in pigmentation by both promoting melanocyte damage and inhibiting melanogenesis, and vice versa by promoting their survival and function of melanocytes (Martinez-Esparza et al., 1998) (Camara-Lemarroy et al., 2013). Furthermore, elevated TNF-α levels in vitiligo lesions suggested a potential role in vitiligo pathogenesis (Camara-Lemarroy et al., 2013). A preliminary report using anti-TNF-α agents for the treatment of generalized vitiligo suggested that depigmentation was stable in 5 out of 6 patients with no new macules (Alghamdi et al ., 2012). Another study suggested the use of TNF-α blockers based on the re pigmentation of vitiligo macules in ankylosing spondylitis patients (Simon et al ., 2008).

Diagnosis

The physical presence of developed, non-scaly, chalky-white macules with transparent edges in a characteristic dispersion in the mouth, tips of the lower extremity, genitalia, and segment and sites of friction usually yields an unambiguous identification of vitiligo (Hara et al .,1996) . Additional chemical testing is usually not required to establish vitiligo identification. A skin biopsy or additional testing is rarely required other than to rule out other illnesses. Non-invasive methods for determining whether a condition lacks melanocytes include in vivo confocal imaging and a skin sample (Hara et al .,1996). According to the histopathology of a vitiligo patch's center, the epidermis's melanin pigmentation has completely disappeared, and no melanocytes are found (Slominski et al ., 2012). Lymphocytes were only occasionally seen at the lesions' expanding edges. Portable ultraviolet (UV) illumination equipment that generates ultraviolet A (UVA), such as a Wood's lamp, could aid in the diagnosis of vitiligo. It aids in the destruction of localized melanocyte and detects regions of depigmentation that may never be visible to human sight, particularly in those with light skin (Slominski et al ., 2012) .Under Wood's light, the vitiligo spots glow brightly blue-white and have distinct borders. Dermoscopy was used to distinguish vitiligo from other depigmenting diseases. Several hypopigmentation syndromes lack residual perifollicular pigmentation and telangiectasia, which are typical vitiligo features. Furthermore, it may aid in determining the stage of development and sickness behavior of vitiligo: Perifollicular pigmentation is seen in progressing lesions, whereas perifollicular depigmentation is seen in static or repatriating lesions (van den Wijngaard et al ., 2000). Vitiligo can be diagnosed in a variety of ways. Hypopigmented areas resembling vitiligo can occur in a variety of common and unusual disorders. It is critical to distinguish vitiligo from melanoma-associated leukoderma and avoid misdiagnosis, primarily because it can occur before melanoma is discovered. Despite having a medically identical appearance, antibodies targeting the melanoma antigen recognized by T cells

1 could distinguish melanoma-associated depigmentation from vitiligo (van den Wijngaard et al ., 2000). Segmental hypopigmentation, also known as nevus depigmentosus , is usually present at birth or during the first year of life. Even though it may change as the child grows, it is consistent. Although nevi frequently have a healthy number of melanocytes with reduced melanin synthesis, it is a distinct differential diagnosis for SV. With Wood's light inspection, the difference between lesioned and healthy skin is less pronounced than in vitiligo (Videira et al .,2003).

Treatment of vitiligo

One of the most challenging dermatological conditions to manage is vitiligo, which requires ongoing treatment. It is essential to recognize that vitiligo is more than a cosmetic concern and to understand that effective treatment options exist—key steps in addressing the condition effectively (Lotti et al ., 2020) . Surgery, local and oral immunosuppressive agents, and phototherapy may all work together to slow the progression of the condition, stabilize hypopigmented lesions, and promote repigmentation. The classification of the illness and its scope, dispersion, and activities, as well as the person's age, phototype, impact on quality of life, and desire for therapy, all influence the medication decision (D'Mello et al., 2016). While the mouth and distal limbs are resistant to treatment, the face, throat, torso, and mid-extremities are the most responsive. Repigmentation occurs around the edges of lesions or in a perifollicular pattern. To determine the effectiveness of a treatment, it must be used for at least two to three months. UV light-based treatments, the most popular vitiligo medication, have been linked to a better outcome when combined with another medication (Park et al., 2003). Treatment necessitates an individualized pharmacological methodology in which individuals must be constantly addressed because most treatment options are time-consuming and require lengthy follow-up. Individuals with vitiligo in visible areas must seek esthetic concealment advice from a licensed cosmetologist or a trained nurse. Selftanning creams containing dihydroxyacetone that provide long-lasting color for up to several weeks, as well as foundation-based beauty solutions, are examples (Bleuel et al., 2018) . The Vitiligo Subcommittee of the European Dermatology Forum has produced standards for the diagnosis and treatment of vitiligo based on the most robust available research and professional advice. The medicines were ranked from first- to fourth-line options. Topical therapies (corticosteroids and calcineurin inhibitors) are first-line treatments. The two second-line therapies are phototherapy (narrow-band ultraviolet B {NB-UVB} and psoralen plus UVA {PUVA}) and systemic steroid management. The third and fourth lines of treatment are surgical grafting methods, including depigmenting therapies (Ezzedine et al., 2015).

Pharmacological management

Topical Treatment Corticosteroids

Corticosteroids have a significant medicinal impact in vitiligo by regulating and suppressing the inflammatory response. Topical corticosteroids (TCS) are the first-line treatment for vitiligo, whether potent (betamethasone valerate) or highly potent (clobetasol propionate). The therapeutic effects are stronger in sun-exposed areas, whereas acral zones typically produce poor results (Westerhof et al .,2000).

Calcineurin Inhibitors

Topical calcineurin inhibitors (TCIs) targeting the head and neck region include tacrolimus (0.03% or 0.1%) and pimecrolimus (1%) (Lotti et al ., 2020) (Ezzedine et al., 2015) , which have fewer adverse effects, particularly no risk of atrophy. For at least six months, TCI could be used twice a day. The course of therapy can be extended if there are visible positive outcomes. During treatment, moderate daily sun exposure is advised (Zhang et al., 2014).

Vitamin D3 Analogues (D3A)

Topical vitamin D3 analogues (D3A) are not effective as a stand-alone treatment for vitiligo due to their immunomodulatory properties, which decrease T cell function, promote melanocyte formation, and induce melanogenesis. Nonetheless, they are useful as supplements to other treatments. The optimum dosage for

four weeks when applying the ointment and eight weeks when applying the cream is 100 g weekly on 30% of the body area, plus a combination of calcipotriol 0.005% and betamethasone 0.05% (Sitek et al., 2006). 5-Fluorouracil (5-FU); methotrexate (MTX); prostaglandin F2 alpha analogues, a peptide derived from primary basic fibroblast growth factor (bFGF); inhibitors of Janus kinase (JAK), systemic therapy corticosteroids; apremilast; etc. are some other promising pharmacological treatments that include minocycline antibiotic use (Sitek et al., 2006) (Faria et al., 2014) (Alikhan et al., 2011).

Topical 5-fluorouracil with microneedling

Microneedling is a minimally invasive procedure now used for multiple dermatologic conditions including vitiligo, which considered a safe and effective technique in treatment of vitiligo either alone or combined with other treatments such as topical 5-Flourouracil, latanoprost, tacrolimus or triamcinolone acetonide solution (Hegazy et al., 2024) (Salloum et al., 2020).5-Flourouracil is an antimetabolite with antimitotic activity, surprisingly used in vitiligo repigmentation which is a process needs melanocyte proliferation. This was firstly introduced by Tsuji and Hamada in 1983 (Tsuji et al., 1983). It was suggested that the inflammatory reaction due to 5-FU application generates mediators as metalloproteinases that stimulate and facilitate melanocyte proliferation and migration, also it was found that melanocytes are less vulnerable to 5-FU than keratinocytes that undergo selective destruction while melanocytes continue to function (Gauthier et al., 2013). With regard to different body sites, 5-FU showed excellent to good improvement in different body sites specially legs and knees 63% **,** arms 45.5% , trunk 25% and one case of foot lesions (25%) showed good improvement (Hegazy et al., 2024).

Physical therapy

Narrow-Band UVB Phototherapy

UV irradiation appears to have several systemic effects, including stimulation of the central hypothalamicpituitary- adrenal axis, initiation of the proopiomelanocortin route in the hypothalamic arcuate nucleus, immunosuppressive effects, and opioid genic outcomes. UVB (wavelength of 280-320 nm) irradiance is more prominent than UVA (wavelength of 320-400 nm) . NB-UVB photodynamic therapy (wavelength of 311 nm) suppresses the immune system, induces melanocyte separation, increases melanin synthesis, and causes melanocyte emigration from perilesional skin to treat vitiligo (Bergqvist et al., 2021).

PUVA

PUVA irradiation (wavelength of 320-340 nm) causes melanin production by suppressing the immune system and fostering an environment conducive to the formation of melanocytes. This second-line treatment usually involves applying psoralen topically or ingesting it and then exposing it to UVA. Psoralens are taken orally for 1-3 hours before UVA exposure (Bergqvist et al., 2020) . Other physical management techniques in use include combined Fraxel Erbium and UVA1 lasers and laser therapy excimer laser (EL) (Boniface et al., 2018).

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