

WHIM Syndrome (*Warts Hypogammaglobulinemia Infections Myelokathexis*)

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Abstract

Whim syndrome is the acronym for Warts, Hypogammaglobulinemia, Infections, Myelokathexis. It is a genetic syndrome with dominant autosomal inheritance characterized by chronic neutropenia associated with bone marrow hypercellularity (myelokathexis). Although the incidence is unknown, this disease is very rare since, up to now, less than 40 cases have been reported. The clinical onset usually occurs during early childhood with recurrent bacterial infections that respond promptly to antibiotic therapy. Later in life most of the patients develop widespread and recalcitrant warts with common Human Papilloma Virus (HPV) serotypes. Cell blood counts show an absolute neutrophil count usually below 300/ μ l, a variable degree of lymphopenia, but normal hemoglobin levels and platelets (both number and volume). Whim syndrome is due to heterozygous mutations affecting the C-terminus of CXCR4, a chemokine receptor mapped on 2q21 locus and expressed by both hematopoietic and non-hematopoietic cells. Treatment consists on monthly injections of Intravenous Immunoglobulin, which may reduce the incidence of infectious episodes. Daily injection of G-CSF or GM-CSF has been observed to normalize neutrophil counts and marrow cytology.

Key words

Neutropenia, recurrent infection, Human Papilloma Virus, CXCR4 receptor, locus 2q21

Name of the disease and synonyms

Warts, Hypogammaglobulinemia, Infections, Myelokathexis;
WHIM syndrome;
Myelokathexis

Definition

Warts, Hypogammaglobulinemia, Infections and Myelokathexis, WHIM (OMIM #193670) is a genetic syndrome with dominant autosomal inheritance. It is characterized by chronic neutropenia associated with bone marrow

hypercellularity (myelokathexis). The disease is due to heterozygous mutations affecting the C-terminus of CXCR4, a chemokine receptor mapped on 2q21 locus(1-4)

Incidence

The incidence of this disease is unknown. In 40 years, since its first description, less than 40 cases have been reported. Distribution is panethnic, with cases described in the USA, Italy, Japan, and Slovenia (4).

Clinical description

The clinical onset of the disease usually occurs during early childhood with recurrent bacterial infections. Infections can be mild to severe, but respond promptly to antibiotic therapy. Respiratory infections (sinusitis, otitis and pneumonia) and cellulitis are common infectious complications. White blood cells (WBC) counts rise in response to acute infection, making it possible to miss the diagnosis during these episodes. Later in life most of the patients develop widespread and recalcitrant warts with common Human Papilloma Virus (HPV) serotypes. Infections with other viral pathogens such as varicella are tolerated without significant complication. Opportunistic infections with viral and fungal pathogens that occur in individuals with more severe immunocompromise have not been reported, suggesting a unique susceptibility to HPV. Extrahematopoietic manifestations are not part of the clinical picture despite the important role of CXCR4 in development, but at least two cases of complex congenital heart disease have been reported in the limited set of described patients, raising the possibility of a causal connection.

Differential diagnosis

The differential diagnosis of WHIM syndrome includes other inherited neutropenias (severe congenital, cyclic) autoimmune neutropenia, and myelodysplastic syndromes. The distinction is generally straightforward based on bone marrow cytology: whereas in WHIM the hallmark is myelokathexis, in the other forms there is absence of mature PMN (Polymorphonuclear Leukocyte), autoantibodies anti-neutrophils, or the presence of non-myeloid lineages abnormalities, respectively. The combination of warts and hypogammaglobulinemia has been described in patients affected by Common Variable Immune Deficiency, but neutropenia is generally not a part of the clinical picture. Severe predisposition to warts occurs also in Epidermodysplasia verruciformis but without the characteristic myeloid and immunological findings of WHIM syndrome.

Methods of biological diagnosis

Cell blood counts show an absolute neutrophil count usually below 300/ μ l, a variable degree of lymphopenia, but normal hemoglobin levels and platelets (both number and volume). Bone marrow aspirates present the pathognomonic findings: myeloid hyperplasia with a shift to the right in granulopoiesis; mature neutrophils display abnormal features such as hypersegmentation of the nuclei and cytoplasmic vacuolization. During systemic infections leukocytosis with neutrophilia is typically

observed. Administration of G-CSF, steroids, or epinephrine also cause a rapid increase in the neutrophil count. Hypogammaglobulinemia is variable and affects all the isotypes. Active immunizations elicit positive responses. By flow cytometry it is possible to detect a decrease in the number of circulating B lymphocytes, with a pronounced reduction of the memory (CD27+) B cell subset.

Etiology

CXCR4 is a chemokine receptor widely expressed by both hematopoietic and non-hematopoietic cells. The ligand CXCL12 or SDF-1 (stromal derived factor 1) is a homeostatic chemokine involved in several physiologic processes and plays a central role in hematopoietic cells homing to and release from bone marrow (5). Neutrophils and lymphocytes from affected patients display an enhanced chemotaxis towards CXCL12 (SDF-1), suggesting that inappropriate retention of mature neutrophils in the bone marrow may underlie the peripheral neutropenia (6).

Prenatal diagnosis

Prenatal diagnosis has not been reported for this condition, but in patients with genotypic information, standard molecular diagnosis can be performed by sequencing from fetal DNA samples. In particular, a recurrent mutation (C1000T) has been detected in several unrelated families.

Management

Monthly injections of Intravenous Immunoglobulin may reduce the incidence of infectious episodes. Daily injection of G-CSF or GM-CSF has been observed to normalize neutrophil counts and marrow cytology (7, 8). Two reports of premature death among young adults with WHIM syndrome have been published. One case was secondary to a bacterial sepsis and the other to a fulminant Epstein Barr Virus (EBV) positive intestinal B cell lymphoma. The latter case and a cutaneous B lymphoma in another patient could suggest an increased morbidity from EBV in WHIM patients (9,10). Warts are generally therapy-resistant, requiring laser ablation for management. The high risk of malignant transformation of genital HPV infection is of concern and requires careful monitoring.

Unresolved questions

The pathogenesis of the disease is still poorly defined, though abnormalities in chemotactic response may play a critical role. The mechanisms resulting in deficiencies of lymphoid cell populations and hypogammaglobulinemia

are still not well understood. Of note, a developmental role for CXCR4/CXCL12 has been suggested in erythrocytes and platelets but these lineages are apparently unaffected in WHIM syndrome. Genetic heterogeneity is suggested by cases of myelokathexis in which no mutations in CXCR4 gene have been identified (2).

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