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WHIM SYNDROME – A LITERATURE REVIEW WITH A DENTAL CONSIDERATION

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ABSTRACT

WHIM (warts, hypogammaglobulinemia, infections, and myelokathexis) syndrome is an autosomal dominant disease related to a mutation in the chemokine receptor CXCR4 resulting in altered immune function. An increased susceptibility in these patients to human papillomavirus (HPV) manifests as cutaneous warts and, in women, cervical dysplasia and squamous carcinoma. Analysis of the myeloid and plasmacytoid dendritic cell blood counts in WHIM patients revealed a striking defect in the number of plasmacytoid dendritic cells as well as a partial reduction of the number of myeloid dendritic cells. Because of the rarity of the disease and the heterogeneity in clinical presentation, diagnosis is often delayed. Here we put forward a review concerning the WHIM syndrome with its dental consideration.

KEYWORDS: WHIM, CXCR4, autosomal dominant syndrome, human papilloma virus, warts, myelokathexis, hypogammaglobulinemia, carcinoma.

INTRODUCTION

WHIM is the acronymic description for a rare autosomal dominant syndrome characterized by warts, hypogammaglobulinemia, infections, and retention of mature neutrophils in the bone marrow (myelokathexis).[1] Firstly in 1964, Zuelzer reported this syndrome in a 10 yr old girl with granulocytopenia and infections.[2,3] Specific mutations identified in WHIM patients include heterozygous C terminus deletional mutations of portions of the intracellular carboxy terminus of the chemokine receptor, CXCR4.[4] The clinical onset and complications in WHIM syndrome (WS) are more variable than originally suspected with the remarkable exceptions of neutropenia and lymphopenia which affects both T and B lymphocytes and NK cells are always observed in patients suffering from this disorder. It is also associated with bone marrow hypercellularity.[5,6] The signature pathogen in WHIM syndrome is human papillomavirus (HPV), which causes warts that cannot be controlled with standard medical treatment and may progress to cancer.[7] According to Jolan E. Walter et al, the incidence of the disease is unclear, with only 109 cases published worldwide in case reports or cohort studies. However, the increasing number of patients diagnosed in recent years suggests that the real incidence of WHIM syndrome may be underestimated.[8] By this background, in the present review we collectively deliberate about WHIM syndrome with its dental consideration.

DISCUSSION

WHIM syndrome is a rare combined immunodeficiency disorder characterized by disseminated human papillomavirus–induced warts, hypogammaglobulinemia, recurrent bacterial infections, and myelokathexis, a form of neutropenia associated with abnormal retention of mature neutrophils in the basement membrane.[9] It is caused by autosomal dominant variants initiating recurrent bacterial infections mainly in the sinopulmonary tract, oral cavity, ear, skin, and soft tissue, where chronic complications may arise, especially bronchiectasis and hearing loss.[10]

Epidemiology: The incidence is still unknown. As it is a rare condition to be reported yet, many authors in the literature have been stated that it is seen in few global parts like, Japan, Europe and Japan.[9] As this syndrome shows the autosomal dominant pattern, it is thought to be affecting both males and females, however, recessive dominant and sporadic forms are also been reported.[5,11]

Etiology

This immune-deficient disease is due to heterozygous mutations affecting the C-terminus of CXCR4, a chemokine receptor mapped on 2q21 locus.[7,12] Further, these mutations affect the intracellular signaling of the receptor in response to the ligand CXCL12.[13,14] Because leukocytes that express CXCR4 have an increased chemotactic response to the CXCL12 ligand, these cells are retained in the bone marrow and lymphoid

compartment forming the complexes, thereby reducing their blood counts.[7,15,16]

This CXCR4-CXCL12 complex has various affects like:[5,14,17,18]

Hematopoiesis of myeloid and lymphopoiesis of B cells.
Organogenesis of cardiac and neural systems.
Gastrointestinal angiogenesis.
Oncogenesis and metastasis of a variety of human neoplasms, including breast and prostate carcinomas, small cell lung cancers, myeloid neoplasms, and pediatric sarcomas.
Human immunodeficiency virus infection, as a coreceptor for the virus.
Chemotaxis of hemato/lymphopoietic cells to lymphoid organs (bone marrow, spleen, and lymph nodes).

The incidence of this disease is mysterious. 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, 15, 19] Most patients with WHIM syndrome are actually panleukopenic, with severely reduced peripheral blood B cells but less severe reductions in peripheral blood T cells and monocytes.[20]

Clinical description

The clinical inception 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.[11] White blood cells (WBC) counts rise in response to acute infection, making it possible to overlook the diagnosis during these episodes.[18] Later in life most of the patients develop pervasive and recalcitrant warts with common Human Papilloma Virus (HPV) serotypes.[21] An increased susceptibility to human papillomavirus (HPV) results in multiple, often disfiguring, cutaneous warts and, in women, susceptibility to HPV-related cervical dysplasia or carcinoma.[1, 21] Infections with other viral pathogens such as varicella are tolerated without considerable complication.[22] The threat for bacterial infections is thought to result from retention of mature neutrophils in the bone marrow (myelokathexis) and consequent unavailability of these cells, manifested as peripheral neutropenia.[13, 15] 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.[2]

The differential diagnosis of WHIM syndrome includes other inherited neutropenias (severe congenital, cyclic) autoimmune neutropenia, and myelodysplastic syndromes.[23] The distinction is generally clear-cut 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.[24] 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.[4, 15]

Cell blood counts show a variable degree of lymphopenia with an absolute neutrophil count usually below 300/µl, but with normal hemoglobin levels and platelets.[25] Bone marrow aspirates often show myeloid hyperplasia with a shift to the right in granulopoiesis; mature neutrophils display abnormal features such as hypersegmantation of the nuclei and cytoplasmic vacuolization. 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.[26, 27]

Dental consideration

Even though cervical dysplasia and squamous carcinoma have been eminent in female WHIM patients, it is imprecise why these patients are susceptible to HPV.[18] In the general population, there is a recently and increasingly recognized association of HPV with squamous carcinomas in the oral cavity. Nicole A. Cipriani et al in 2010 reported the occurrence of HPV-related squamous cell carcinoma of the oral cavity in 2 siblings with WHIM syndrome, whose pedigree has previously been described.[2] The identification of high-risk HPV and p16 oncoprotein in these cases suggested but couldn't prove an etiologic role of the virus in carcinogenesis, because not all lesions with HPV progress to carcinoma. Some studies put forward that synchronized use of tobacco or alcohol might increase the risk for carcinoma in patients who are already HPV positive.[28, 29] Inside beam of such a "2-hit" hypothesis, the immune dysfunction precipitated by WHIM syndrome might serve as the second hit in patients with oral HPV, further increasing their risk for squamous carcinoma.[2, 21]

Treatment

The therapeutic management of these patients is diverse. Some patients have no prophylactic therapy, while others may receive prophylactic antibiotics or antiviral therapies such as Immunoglobulins (Ig), Granulocyte macrophage colony-stimulating factor (GMCSF),

Granulocyte colony-stimulating factor (GCSF) and eventually undergo hematopoietic stem cell transplantation, however, long-term efficacy remains undefined.[22, 23, 30] 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.[20, 25]

Prognosis

Patients could have a shorter life span due to recurrent infections and increased risk of malignancy; the oldest reported age identified is a 75-year-old patient. In a report of 60 cases of WHIM syndrome, five deaths were identified (83%) aside from one case of medically aborted fetus with cardiac anomaly; two died of lymphoma when age 26 and 54 years, one died of mycobacteria-related liver failure (with underlying lymphoma) at 40 years old, one died of advanced HPV-related genital disease at the age of 395 years, and one due to bacterial meningitis when aged 31 years.[23] The risk of malignancy in these cases was estimated at 30% by the fourth decade, with the onset being shortly beyond the third decade.[31] Improved quality and span of life could be expected with early recognition, controlling infections and preventing malignant transformation in addition to targeted and supportive treatments in order to decrease the fatality.

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Improved quality and span of life could be expected with early recognition, controlling infections and preventing malignant transformation in addition to targeted and supportive treatments in order to decrease the fatality.

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