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Review Article

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Neutrophil associated syndromes and periodontitis

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ABSTRACT

The tissue destruction characteristic of periodontal diseases is a result of an imbalance between the host inflammatory process and specific pathogenic bacteria residing in the periodontal crevicular space. The protective nature of the host response enables the majority of the population to defend the bacterial insult that constantly threatens the health of the supporting tissues of the dentition. One of the major players on this inflammatory and immunologic battleground is the polymorphonuclearleukocyte (PMN) or neutrophil. A general knowledge of these syndromes is of benefit in understanding the role the neutrophil holds in the initiation and progression of periodontitis and in coordinating the multidisciplinary care that is often required. Aim of this article is to review those syndromes that have a link between neutrophil dysfunction and periodontitis.

Key words: PMNs/ neutrophils, periodontitis, syndromes

INTRODUCTION

Periodontal diseases are infectious diseases resulting from the interactions of oral bacteria residing in dental plaque and the host [1].The immune system is a complex, highly regulated set of processes that require the host to detect changes in host cells or unwanted exogenous cells [2] . Neutrophils form the first line of defence of the human innate immune system. These myeloid-derived, professional antimicrobial phagocytes can kill pathogens extracellularly, links innate and adaptive arms of the immune response, and help to endorse the inflammatory resolution and tissue healing [3].As evidence, individuals with defects in neutrophil function or biochemistry often show severe forms of periodontal disease and, on the contrary, individuals with early onset or rapidly progressing forms of periodontal disease often exhibit neutrophil defects [4].

Investigators have demonstrated defective neutrophil function in a number of patients with LJP who otherwise appear healthy.

Syndrome is defined as a group of symptoms and signs of disordered function to one another by means of some anatomical, physiological, or biochemical peculiarity [5].There are various syndromes with diverse manifestations affecting the body including the oral cavity and periodontal tissues. This review attempts to gives a concise update on syndromes with neutrophil abnormalities associated with periodontitis.

ROLE OF NEUTROPHILS:

Since neutrophils are not concerned with their own survival, they are free to use delivery modes which can be suicidal. Neutrophils deliver antimicrobial substances by different mechanisms

1. **Adherence** — When stimulated, the neutrophil interacts with, and sticks to, substrate (endothelial cells) via specific molecules on the neutrophil and the endothelial cell.
2. **Chemotaxis-** Neutrophils migrate to sites of bacterial ingress or tissue damage through the process of chemotaxis. The term chemotaxis was introduced in 1884 by Pfeffer, who described it as directional migration of leukocytes along a chemical gradient [6].
3. **Opsonization** & **Phagocytosis**- The neutrophil recognizes specific molecules on the bacterial surface called opsonins (IgG, C3b) and engulfs the bacteria. Phagocytosis is the engulfment of particles within a membrane-bound structure called the "phagosome." Fusion between the cytoplasmic granules (lysosomes) and the phagosome form the "phagolysosome," and represent a specialized form of secretion [7].
4. **Bacterial Killing** – The neutrophil is responsible for bacterial killing by 2 pathways for controlling microorganisms - oxygen dependent and independent mechanisms.

NEUTROPHIL DEFECTS:
Being the most important phagocytic cell in the defence of the host against acute bacterial infection, disorders of neutrophil function are suggested by recurrent cutaneous, periodontal, respiratory, or soft-tissue infections. *Staphylococcus aureus*, gram-negative bacilli, and, less commonly, *Candida albicans* are the causative organisms.
Neutrophils disorders may be-

I. Quantitative Neutrophil Defects:

A. Neutrophilia- Increased count of circulating neutrophils
Quantitative defects can be at the bone marrow like in Kostman syndrome (OMIM-Online Mendelian Inheritance in Man 610738) and Felty's syndrome or at the periphery as in Lazy leukocyte syndrome. Other syndromes that are associated with decreased neutrophil counts and periodontal destruction include Herman sky–Pudlak syndrome and Shwachman–Diamond syndrome. All syndromes present with wide spread and early periodontal tissue destruction.

B. Neutropenia- Decreased count-A relative deficiency in neutrophil number can dramatically increase susceptibility to infectious diseases.
Defects in the functions of neutrophils or a marked decrease in the number of neutrophils capable of responding to the site of infection may result in varying degrees of susceptibility to infection [9].

There are three general guidelines used to classify the severity of neutropenia based on the Absolute Neutrophil Count (ANC) measured in cells per micro liter of blood:
- Mild neutropenia (1000 <= ANC < 1500) — minimal risk of infection
- Moderate neutropenia (500 <= ANC < 1000) — moderate risk of infection
- Severe neutropenia (ANC < 500) — severe risk of infection

II. Qualitative Neutrophil Defects
These can be defects in rolling and adhesion (Leukocyte adhesion deficiency syndrome), defects in migration and chemotaxis (Hyperimmunoglobulin E syndrome), lazy leukocyte syndrome, Papillon-Lefvre syndrome, Down's syndrome, Kindler syndrome) and defects in phagocytosis and intracellular killing (Chediak Higashi syndrome) [9]. These include the following:

CHEDIAK-HIGASHI SYNDROME
Chediak-Higashi syndrome is a rare autosomal recessive disorder that primarily affects neutrophils [10]. Its genetic etiology manifests itself early in life in the form of partial oculocutaneous albinism, photophobia, frequent pyogenic infections and lymphadenopathy.

Clinical Features: The syndrome may present as abnormalities of pigmentation, recurrent infections, and bleeding tendencies [16]. Oculocutaneous albinism can affect the skin, eyes, and hair. Hair colour is characteristically metallic silver, the skin colour white to gray due to defective melanosomes, and the eyes are affected by reduced pigmentation of the retina and iris. Other ocular abnormalities can include nystagmus, photophobia and reduced visual acuity. Infections are commonly skin abscesses, pneumonias, otitis media and sinusitis. Bleeding problems arise because of organelle abnormalities within platelets that inhibit normal clot formation [16]. Weakness, sensory deficits, clumsiness, a wide-based gait, seizures and tremors have also been reported [12].

The average lifespan for children with Chediak- Higashi syndrome is only 6 years [13]. The few individuals that do survive beyond the first decade often progress to a lymphoma-like disease known as the accelerated phase. This phase can include fever, jaundice, hepatosplenomegaly, and pancytopenia that lead to an even greater susceptibility to infection [10].

On a cellular level, organelle abnormalities, specifically of lysosomes, are present in cells throughout the body [14]. One of the hallmarks of the Chediak- Higashi syndrome is the presence of large intracellular azurophilic inclusions in the cytoplasm of neutrophils.

These large inclusions impair neutrophil migration, possibly by inhibiting cell deformability
[16], and render neutrophils unable to metabolize and digest microbes. As a result, patients with Chediak- Higashi syndrome are prone to recurrent infections in early childhood [13]. Animal research has led to the determination that a mutation in the LYST (lysosome trafficking regulation) gene, the only known Chediak-Higashi syndrome-causing gene, may be responsible for this phenomenon [12].

Oral findings include severe gingivitis, ulcerations of the tongue and buccal mucosa, and early onset periodontitis leading to premature loss of both deciduous and permanent dentitions [17].

LEUKOCYTE ADHESION DEFICIENCY (LAD):
Leukocyte adhesion deficiency is a very rare genetic disorder. Two types of leukocyte adhesion deficiencies, LAD-I and LAD-II have been identified

LAD I:
LAD-I is an inherited disorder that follows an autosomal recessive pattern (Chromosome 21q22.3).

LAD-I is a disorder that involves a deficiency in three membrane integrins. CD18/C11a (LFA-1) binds to leukocytes and to endothelium via intercellular adhesion molecules (ICAM). CD18/CD11b (Mac-1) binds to ICAM and complement and facilitates complement-mediated phagocytosis. The function of the third integrin, CD18/C11c is not well understood.

The deficiency of these integrins prevents the neutrophil from adhering to the vessel wall at the site of an infection. Therefore, inspite of a leukocytosis (20,000–80,000 cells/ml), neutrophils are unable to migrate into the affected tissues.

Clinical Features:
These patients also have frequent respiratory tract infections and sometimes otitis media

Oral manifestation: The children may present with acute gingival inflammation of both primary and permanent dentitions, as well as gingival proliferation, recession, tooth mobility, and pathologic migration. Both primary and permanent teeth may be affected, often resulting in early tooth loss [8, 9].

LAD II:
The neutrophil defect in LAD-II is of the sialyl-Lewis x glycoprotein (CD15s), which allows neutrophils to attach to selectins (CD62E) on the endothelial surface. The neutrophils are unable to migrate extravascularly as in LAD I [8]. While the oral condition of these patients has not been reported, it can be assumed that the neutrophil defect is such that severe periodontal disease and tooth loss is likely.

Aggressive periodontitis at early age and tooth loss is likely.

PAPILLON LEFEVRE SYNDROME:
It is a very rare inherited condition that appears to follow an autosomal recessive pattern and a prevalence of one to three cases per million in the general population.

PLS is caused by mutations in the cathepsin C gene, located on chromosome 11 (11q14-q21) [13].

Clinical Features:
Ectopic calcifications of the falx cerebri and choroid plexus, increased susceptibility to infection, mental retardation, and endocrine disorders have been reported in this syndrome.

Oral manifestations: It is characterised by a diffuse palmoplantar keratosis associated with aggressive periodontitis of both primary and permanent dentitions and in some cases, calcification of the dura.

The two essential features of Papillon - Lefe`vre syndrome are hyperkeratosis of the palms and soles (either diffuse or localized) and generalized rapid destruction of the periodontal attachment apparatus resulting in premature loss of both primary and permanent teeth.

Papillon-Lefe`vre syndrome is also associated with aggressive periodontitis.

A particular form of Papillon-Lefe`vre syndrome has been named the **Haim-Munk syndrome.** While also characterized by palmoplantar keratosis and severe early onset periodontitis, the Haim-Munk syndrome additionally presents with digital abnormalities. A decrease in the chemotactic activity of neutrophils, as well as decreased phagocytosis and intracellular killing of certain bacteria in Papillon-Lefe`vre syndrome patients have been reported Alterations in cementum, an imbalance of collagenolytic activity in the periodontal ligament, and an increased osteoclastic activity in some Papillon-Lefe`vre syndrome patients are reported [23].

FELTY'S SYNDROME:
Felty's syndrome is an uncommon complication of rheumatoid arthritis, in which splenomegaly and leukopenia are the major additional features [25]. The incidence of Felty's syndrome is in about 1% of all rheumatoid arthritis cases [26].

Clinical Features:
In addition to the distinguishing triad of symptoms i.e. rheumatoid arthritis, splenomegaly and leukopenia, other recurring signs and symptoms including weight loss, progressive weakness, hyperpigmentation of the skin, generalized lymphadenopathy, hepatomegaly, increased susceptibility to infection, and a variety of abnormalities in white blood cell count and function [28].

The leukopenia noted in Felty's syndrome is primarily due to a lack of circulating neutrophils. Several mechanisms have been suggested to explain this phenomenon, including insufficient formation of neutrophils, reduced release of neutrophils from the bone marrow, a shortened neutrophil life span, and excessive neutrophil margination [29].

Oral manifestations: While oral ulceration and ''stomatitis'' are frequently mentioned in reports of Felty's syndrome [30, 31], periodontitis has only rarely been implied [31]. Even so, it can be assumed that with the dramatic deficiency in circulating neutrophils noted in some patients, the incidence of periodontitis is as at least as great in Felty's syndrome patients as in others with severe neutropenia.

DOWN'S SYNDROME (Mongolism, trisomy 21)
Down's syndrome, is a congenital disease caused by a chromosomal abnormality and is one of the most common causes of mental retardation in children, was named after the English physician who in 1866 characterized the appearance and behavior of these patients.

Clinical Features: Mental retardation (Mild to severe with an IQ 25-50), brachycephaly, hypertelorism, depressed nasal bridge, flat occiput, and broad short neck.

Ocular anomalies: Narrow, upward and outward slanting of the palpebral fissures, medial epicanthal folds, strabismus, cataract and retinal detachment

Skeletal anomalies : short stature, broad and short hands, feet, and digits; short curved fifth finger, clinodactyly of the fifth finger; dysplasia of pelvis; joint laxity; a wide gap between first and second toes. Muscle hypotonia in newborns with decreased response to normal stimuli has been reported.

Protuberant abdomen, hypogenitalism, hypospadia, cryptorchism and delayed and incomplete puberty. Congenital defects of the heart, or endocardial defects have been observed.

Oral Manifestations: Increased incidence of periodontal disease (occurring in almost 100% of patients younger than 30 years) ranging from severe gingivitis in the youngest patients to periodontitis with pocket formation and alveolar bone loss in the older patients. Although, plaque, calculus, and local irritants (eg. diastemata, crowding of teeth, high frenum attachments, and malocclusion) are present and oral hygiene is poor, the severity of periodontal destruction exceeds that explainable by local factors alone.

In an extensive review of periodontal disease in Down's syndrome, Roland-Bousma & Van Dijk [32] examined both endogenous conditions and exogenous factors that may predispose affected patients to aggressive periodontitis.

Among the endogenous factors that may exacerbate the periodontitis in Down's syndrome are defects in neutrophils. The first cellular anomaly linked to Down's syndrome was the tendency of the nucleus in neutrophils of Down's syndrome patients to be consistently less segmented than in other patient groups [33]. Neutrophil chemotaxis defects and reduced bactericidal capacity has been reported for a number of organisms, including S.aureus, Escherichia coli, and C. albicans [34].

LAZY LEUKOCYTE SYNDROME

Lazy leukocyte syndrome is a very rare disorder that manifests in both quantitative and qualitative neutrophil defects. It is characterised by susceptibility to severe microbial infections, and an abnormal inflammatory response [35].

Clinical Features: It has recurring infections due to both a deficiency in neutrophil chemotaxis and a systemic neutropenia, while the phagocytic function of the neutrophil remains intact [35]. Within the bone marrow, the quantity and morphology of the neutrophils are normal. Peripherally, on the other hand, there exists not only a severe neutropenia but also functional defects of neutrophils with regard to chemotaxis and random migration. The abnormal function of these microfilaments leads to a defect in cell deformability, and this hinders the release of newly formed neutrophils from the bone marrow [36]. Impaired random and directional motility leads to a diminished in vivo migration of neutrophils into the tissue and to sites of inflammation.

Oral Manifestations: Painful stomatitis, gingivitis and recurrent ulcerations of the buccal mucosa and tongue. Periodontitis progressing to the point of advanced alveolar bone loss and tooth loss has been reported. Individuals diagnosed with lazy leukocyte syndrome are susceptible to aggressive periodontitis [35].

CONGENITAL NEUTROPENIA (KOSTMANN SYNDROME)

Congenital neutropenia is a very rare (1-2 case per million) inherited hematologic disorder. In most cases of congenital neutropenia, the underlying mechanism of the syndrome is unknown.
Clinical Features: Manifests in the first year of life and is characterized by severe bacterial infections.

While most of the originally reported cases died in infancy, aggressive treatment with antibiotics has more recently prolonged the lifespan of children suffering from this disease [37]. (The significant laboratory findings are an absolute neutrophil count of less than 2,000/ml and an arrest of neutrophil hematopoiesis at the promyelocyte/myelocyte stage).

Oral manifestations: Oral symptoms are virtually universal in congenital neutropenia. In a recent report by Carlsson & Fasth [37], all of the patients that survived infancy were affected by gingivitis, and most were noted to have periodontitis with alveolar bone loss. Another recent case report demonstrated generalized severe periodontitis in an adolescent patient with congenital neutropenia [38].

HYPERIMMUNOGLOBULIN E SYNDROME:

Hyperimmunoglobulin E syndrome is a multisystem disorder inherited as an autosomal dominant trait that affects the dentition, the skeleton, connective tissues, and immune system. In hyperimmunoglobulin E patients, a defect in neutrophil chemotaxis contributes to the high rate of recurrent infections [39].

Clinical Features: It has been characterized by a triad of symptoms including skin abscesses, pneumonia, and elevated serum immunoglobulin E levels [40]. Eosinophilia, candidiasis, arthritis, chronic eczematoid dermatitis and other recurrent infections are also common [41].

Typically, patients with hyperimmunoglobulin E syndrome have coarse facial skin with prominent pores. Other common findings include facial asymmetry, prominent forehead, deep-set eyes, broad nasal bridge and mild prognathism. A decrease in bone density is common, leading to a high incidence of long bone fractures [41].

Clinically, the appearance of the soft tissue lesions is rather unique. Often described as ‘‘cold abscesses’’, these deep soft tissue lesions present as fluctuant masses that may be mistaken for cysts or tumors. These abscesses, typically caused by S. aureus, often lack the usual signs of inflammation, such as warmth, erythema, and tenderness. Extension of these lesions into bone may occur giving rise to an osteomyelitis [42].

Recurrent infection is one of the chief features of hyperimmunoglobulin E syndrome.

Certainly contributing to the high rate of recurrent infections in hyperimmunoglobulin E patients is a defect in neutrophil chemotaxis [41].

Oral manifestations: In hyperimmunoglobulin E patients include ulcerations and gingivitis. An increased susceptibility to severe periodontitis would definitely be consistent with the neutrophil defect seen in patients with hyperimmunoglobulin E.

CONCLUSION

Certain periodontal diseases may represent the failure of specific neutrophil immune mechanisms which control specific periodontopathic bacteria and specific subsequent chronic inflammatory responses. Impaired neutrophil functions as well as impaired functions of other cells of the host response are a central mechanism in the progression of chronic and aggressive forms of periodontitis. The knowledge of these syndromes is essential as they can influence the prognosis and management of periodontal disease.

Thus, neutrophils constitute the non-specific yet most prompt and effective response to infection. The abnormalities of neutrophilic function are strongly implicated in the pathogenesis of certain aggressive forms of periodontal diseases. Study of distortion of neutrophil function in terms of defect or hyperactivity forms an intriguing research topic. Also with the advent of advanced diagnostics in periodontics, the quantitative and qualitative evaluation of neutrophils forms can open up new avenues in diagnostic research. Hence it is important to know the functions of these cellular sentinels and their role on periodontal disease.

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