

## Review Article

# Oral manifestations associated with neutrophil deficiency and neutrophil disorders: A review

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	International Archives of Integrated Medicine, Vol. 5, Issue 6, June, 2018.	
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	Available online at <a href="http://iaimjournal.com/">http://iaimjournal.com/</a>	
	ISSN: 2394-0026 (P)	ISSN: 2394-0034 (O)
	Received on: 09-05-2018	Accepted on: 14-06-2018
	Source of support: Nil	Conflict of interest: None declared.
<b>How to cite this article:</b> Archana Tangudu, B. Badari Ramakrishna, K.V.S.P. Gupta, M.V. Mrudula, Rahul Marshal Vaddeswarapu. Oral manifestations associated with neutrophil deficiency and neutrophil disorders: A review. IAIM, 2018; 5(6): 61-71.		

## Abstract

The immune system evolved to protect multicellular organisms from pathogens. It defends the body against invaders, and generates an enormous variety of cells and molecules capable of specifically recognizing and eliminating foreign invaders, all of which act together in a dynamic network. Neutrophils have been referred to as a first line of defense, meaning that they are first defensive cells to be recruited to a site of inflammation; however the resident leukocytes are cells which normally exist at the sites of inflammation. Neutrophils exhibit their antibacterial action with the help of granules or by virtue of its ability to reduce dioxygen to hydrogen peroxide. The primary mission of neutrophils is to find bacteria and neutralize them by phagocytosis.

## Key words

Periodontitis, Neutrophils, Phagocytosis, Neutropenia, Gingiva.

## Introduction

The strategy of host defense against periodontal infection may be viewed as similar to that used in combating any local infection. Initially, potential periodontal pathogens encounter plasma factors, such as complement, within the crevicular or extracellular fluids. The result of this encounter is the initiation of inflammatory processes, as evidenced by the recovery of complement activation products from the gingival crevice. If complement is not successful in controlling the pathogen, the host defense turns to “Phagocytes” [1].

Phagocytes are cells which ingest particles visible to light microscopy. The process of eating particles is called “Phagocytosis”, a process which is considered as one of the distinguishing features of eukaryotic cells, found even in such primitive organisms as the amoeba, which hunt, ingest and kill microbes for nutritional purposes. Many cells in our body are capable of phagocytosis, but only two are good enough to be considered professional [2].

1. Neutrophilic polymorphonuclear leukocytes ( PMNs)
2. Monocytes / Macrophages

Neutrophils, monocytes and other granulocytes form the myeloid arm of the immune system. The lymphoid arm includes T-Cells, B-Cells and large granular lymphocytes (Natural Killer cells). Bone marrow stem cells give rise to both cellular arms in a teeter – totter fashion [1].

Neutrophils within the gingival crevice provide the first cellular host mechanism to control periodontal bacteria. They bring an astounding arsenal of antimicrobial weaponry packed within almost all of their cellular compartments (like calprotectin complex, lysozyme, defensins, cofactor – binding proteins, neutral serine proteases, bactericidal/permeability increasing protein, myeloperoxidase and a NADPH oxidase system). If neutrophils are unsuccessful in controlling the pathogen (reducing bacterial antigen levels sufficiently), monocytes are

recruited which infiltrate the connective tissue, develop into tissue macrophage and either digest the antigen completely (and signal repair processes with cytokines such as transforming growth factor  $\beta$ ) or present partially digested antigen in association with Major Histocompatibility Complex (MHC) encoded class II molecules to lymphocytes [1].

Perhaps to avoid systemic infections, chronic periodontal inflammation may produce localized specific immune responses and a cytokine – orchestrated destruction of connective tissue which we call “Periodontal Disease”. Thus, neutrophils are important because they control the periodontal micro-ecology prior to the involvement of chronic inflammatory cells. According to the acute and chronic immune elements, it may be proposed that specific periodontal disease can result from the failure of specific aspects of host immune system (neutrophil in particular) in its interaction with specific periodontal pathogens. Simplistically, either hypofunction of neutrophils or hyperfunction of monocytes / lymphocytes may result in increased susceptibility to periodontal diseases [1, 2].

As evidenced, individuals with defects in neutrophil function or biochemistry often exhibit severe forms of periodontal disease and conversely, individuals with early onset or rapidly progressing forms of periodontal disease often exhibit relatively subtle neutrophil defects. These defects can be primary or secondary in origin. Primary defects are actual defects of neutrophils namely Neutropenia, Agranulocytosis, Chediak – Higashi syndrome, Lazy Leukocyte syndrome. Secondary disorders are seen in individuals with Down syndrome, Papillon – Lefevre syndrome and Inflammatory Bowel Disease etc.

This review would give an insight into neutrophils functions, their role in host defense mechanism, neutrophils disorders and their association with periodontal diseases.

## **Neutrophils and The Periodontal Inflammatory Lesion**

The periodontal lesion is characterized by large proportions of inflammatory cells and the vascular structures. Neutrophils predominate in the early periodontal lesion that characterizes gingivitis. However, the relative proportion of neutrophils in the inflammatory infiltrate decreases during the transition to periodontitis in which plasma cells and lymphocytes are dominant. It was reported that plasma cells occupied 31% of the periodontitis lesion volume, while the proportion of lymphocytes varied between 5% and 10%. Macrophages and neutrophils were found in densities of 1-2% and fibroblasts in 5% [3, 4].

Neutrophils may be especially important during the transition from gingivitis to periodontitis. Furthermore, they may play a role in the pathogenesis of periodontitis in the gingival crevice and in the epithelium, where they are the dominant inflammatory cells. The early, nonspecific neutrophil response to dental plaque organisms (both the pathogenic and non pathogenic) allows pathogenic bacteria to proliferate and invade, setting the stage for the transition from gingivitis to periodontitis [2, 3].

## **Neutrophil Disorders Predispose To Periodontitis**

Disorders that affect neutrophil number or function strongly predispose individuals to infection. Neutrophil disorders can be divided into those that affect neutrophil number, chemotaxis, and various physiological functions of the neutrophil once it has migrated to the site of inflammation [5]. Naturally occurring neutrophil disorders can relate biochemical pathways to the resulting clinical manifestations of disease. Such functional disorders of neutrophils predispose to recurrent cutaneous, respiratory and periodontal infections. The fact that quantitative or qualitative defects in neutrophil function may lead to severe periodontal breakdown supports the central role of these cells in protecting the periodontium in

health, when a constant bacterial burden is present [6].

## **Neutrophil Disorders In Periodontitis pathogenesis In Otherwise Healthy Subjects**

Neutrophil dysfunctions have a strong effect on the ability of the host to cope with infections, including periodontal infection. However, the role of intrinsic or acquired neutrophil defects in the periodontal environment of otherwise healthy subjects is much less straight forward. Most of the data on neutrophil disorders in otherwise healthy subjects were accumulated on young patients with early onset forms of periodontitis i.e., aggressive periodontitis. Early studies demonstrated that peripheral neutrophils of patients with aggressive forms of periodontitis exhibited reduced chemotaxis in response to chemotactic signals in vitro and in vivo (Ryder 2010) [2, 3, 6]

The evidence that specific variants in neutrophil function contribute to periodontitis in otherwise healthy individuals is low. Early studies had demonstrated differences in chemotaxis and reactive oxygen species production (ROS) and considered them as “Neutrophil Defects”. However, today these results are interpreted as “neutrophil hyperresponsiveness”. It is possible that in some cases genetic polymorphisms may contribute to pathogenesis in a minority of aggressive or chronic periodontitis cases [5].

## **Chronic Benign Neutropenia**

Chronic benign neutropenia is characterized by a prolonged non cyclic neutropenia as the sole abnormality, with no underlying disease to which the neutropenia can be attributed.

- It is the most common form of neutropenia of infants and children less than 4 years of age, with 90% of the cases presenting before 14 months of age.
- The incidence of chronic benign neutropenia is 3.9 per 1,00,000 births.

- It is usually not inherited; however the familial form follows an autosomal dominant mode of inheritance [7, 8].

### **Familial Chronic Benign Neutropenia**

It was first reported by Glansslen in 1941, and then by Bousser et al. in 1947. The clinical presentation can be quite variable, from a benign condition discovered incidentally to an early life threatening infection, but most patients with chronic benign neutropenia will live a normal life span. Individuals may suffer from increased incidences of recurrent oral ulcerations, furuncles, upper respiratory tract infections, otitis media, cellulitis, lymphadenopathy, pneumonia and sepsis as a result of the limited neutrophil response to infection. As these individuals get older, the risk of infection appears to decrease [8].

Oral manifestations of chronic benign neutropenia include hyperplastic, edematous and fiery-red gingiva with areas of desquamation [7, 9].

### **Cyclic Neutropenia**

Cyclic neutropenia is a rare blood disease characterized by periodic recurring symptoms of fever, malaise, mucosal ulcers and possibly, life threatening infections related to the regular cyclical fluctuations in the numbers of neutrophils. The disease is transmitted as autosomal dominant mode of inheritance. Its incidence is 0.5 – 1 per million population. The bone marrow may appear hypoplastic with promyelocytic arrest during periods of neutropenia. Lots of promyelocytes and very few numbers of mature cells are seen. Cyclic neutropenia has got both childhood and adult onset. Childhood onset is more common and appears in familial pattern of inheritance whereas the adult onset is rare [7].

This condition was first reported by Leale in 1910, who described a persistent furunculosis in an infant. Cyclic neutropenia usually presents before the age of 10 years, with episodes of fever, malaise, mood swings and oral ulcerations that can last 3-6 days and recur approximately

every 3 weeks. The interval between neutropenic episodes is not always obvious and may require frequent laboratory tests. The disease tends to improve with age although death can occur in as many as 10 % of affected individuals as a result of pneumonia, cellulitis, gangrene or peritonitis [7, 10].

A recent description of 2 years old child presented with recurrent gingivitis and apthous lesions. Clinically, no recession was noted and probing depths were within normal limits. Analysis of microbial flora found *P.intermedia*, *Campylobacter rectus*, *Capnocytophaga gingivalis* and *C.sputigenis*. In spite of treatment, the child continued to experience gingivitis during 2 years of follow-up. Numerous other case reports have been documented marked gingival inflammation, fever, oral ulcerations, otitis media, upper respiratory infections associated with cyclic neutropenia. Unfortunately, even with the best of professional care, teeth are often lost due to advancing periodontal disease [10].

### **Congenital Neutropenia**

Congenital neutropenia is also called as “Kostmann Syndrome” which was named for the Swedish pediatrician who first described the disease in 1950. It is an inherited hematologic disorder manifesting in the first year of life and characterized by severe bacterial infections. The significant laboratory findings are an ANC <2,000 cells / $\mu$ l and an arrest of neutrophil hematopoiesis at pro-myelocyte / myelocyte stage. The estimated frequency is 1 or 2 cases per million in general populations with no sex predilection. Though the disease was originally described to be inherited as autosomal recessive trait, the diagnosis is now used for similar cases without a defined pattern of inheritance [7].

In most of the cases of congenital neutropenia, the underlying mechanism of the syndrome is unknown. Oral symptoms are universal in congenital neutropenia. In a recent report by Carlsson & Farth, all the subjects that survived infancy were affected by gingivitis and most

were noted to have periodontitis with alveolar bone loss. Another case report demonstrated generalized severe periodontitis in an adolescent patient with congenital neutropenia. In most of the cases even after the treatment there was persistent gingivitis [5].

### **Agranulocytosis**

Agranulocytosis is a blood dyscrasia characterized by a decrease in or even the disappearance of granular leukocytes (including neutrophils) in conjunction with peripheral leukoplakia [11].

The decreased number of neutrophils can result from either a decreased production of cells, or an increased peripheral destruction of cells. Decreased production is usually due to bone marrow hypoplasia, although drugs, chemicals, ionizing radiation, infection, vitamin deficiencies and bone marrow tumors can cause similar effects.

Oral manifestations -Generalized, painful stomatitis, spontaneous bleeding and necrotic tissue. Radiographs generally reveal a progressive pattern of bone loss at an early age. Depending on the cause and duration, severity varies [7].

### **Felty's syndrome**

The leukoplakia noted in Felty's syndrome is primarily due to a lack of circulating neutrophils (neutropenia). This neutropenia may be due to insufficient formation of neutrophils, reduced release from bone marrow, shortened neutrophil life span and excessive neutrophil margination. Breedveld et al. monitored a variety of hematologic parameters in a group of 15 patients at 3 months intervals for 3 years. The authors determined that the risk of infection was best correlated with neutrophil cells [7].

Oral ulceration and stomatitis are frequently occurring manifestations. Periodontitis has only rarely been reported. Even then, it is assumed that with the dramatic deficiency in circulating neutrophils in some patients, the incidence of

periodontitis is at least as great in Felty's syndrome patients as in others with severe neutropenias [7].

### **Lazy leukocyte syndrome**

Lazy leukocyte syndrome is an extremely rare disorder that manifests in both quantitative and qualitative neutrophil defects. It is characterized by recurrent infection due to both a deficiency in neutrophil chemotaxis and a systemic neutropenia, while the phagocytic function remains intact. Within the bone marrow, the quantity and morphology of the neutrophils are normal. Peripherally, however, there exists not only a severe neutropenia but also functional defects of neutrophils with regard to chemotaxis and random migration [2, 5, 7].

Oral manifestations -Very few case reports have been reported, but each has had oral manifestations. Constantopoulous et al. described a 5 month old boy who presented with high fever, cough, bilateral pneumonia, oral stomatitis and purulent skin abscesses. Laboratory tests revealed a peripheral neutropenia, and impairment of both neutrophil chemotaxis and random motility. Another case report was of a 4 year old child with Lazy leukocyte syndrome and followed over 7 years. The boy suffered from painful stomatitis, gingivitis and recurrent ulcerations of the buccal mucosa and tongue. Periodontitis progressed to advanced alveolar bone loss and tooth loss by the age of 7. The prognosis for the dentition of patients with lazy leukocyte syndrome appears poor [7].

### **Leukocyte adhesion deficiency (LAD)**

In 1979, a group of patients with similar symptoms of delayed umbilical cord separation and persistent bacterial infections in the absence of pus formation were found to share a common neutrophil motility defect. The name leukocyte adhesion deficiency syndrome was given to this condition by Anderson & Springer in 1986 [5].

Leukocytes are known to adhere to vessel wall endothelium, other leukocytes and to complement via cell surface integrins. These

integrins are protein complexes that are stored within neutrophil granules and when activated, are found on the surface of neutrophil cell membranes. The initial study on leukocyte adhesion deficiency patients found a defect in the neutrophil integrins CD11 & CD18. Subsequent investigations into this disorder have identified two types of leukocyte adhesion deficiency disorders [12].

#### **Type I:**

It is an autosomal disorder (localized to chromosome 21q22.3) characterized by the inability of individuals to express  $\beta_2$  subunit (CD18) common to the leukocyte integrins LFA-1, Mac-1 & GP 150/95. LAD-I is a disorder that involves a deficiency in three membrane integrins as mentioned earlier. CD18/CD11a (LFA-1) binds to leukocytes and to endothelium via intercellular adhesion molecules (ICAM). CD18/CD11b (Mac-1) binds to ICAM and complement facilitates complement mediated phagocytosis. The function of the third integrin CD18/CD11c 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, in spite of leukocytosis (20,000 – 80,000 cells / $\mu$ l) neutrophils are unable to migrate into the affected tissues[12].

There have been just over 600 cases described, each identified shortly after birth. More than 75% of children will die before the age of 5, if they do not receive a bone marrow transplant. The severity of the disease is based on the relative expression of CD18. Less than 1% of normal is described as severe, while 2.5 – 10% is considered as moderate to mild. Periodontal disease is related to whether one or two defective alleles are present. Homozygotes exhibit generalized pre pubertal periodontitis (GPP) which affects both deciduous and permanent dentition. Heterozygotes appear to have normal pre pubertal periodontal status. However, “post-LJP-like” lesions appear at some point post pubertally. Few studies that associate GPP with LAD-I tend to suggest that LAD-a is the only

contributor to GPP, which may not necessarily be true and several congenital neutrophil defects have been associated with severe periodontitis [11, 13].

#### **Type – II:**

LAD-II was first described in 1992 by Etziomi, et al. Only 4 cases have been documented of this type. Individuals with LAD-II are characterized by short stature, mental retardation and craniofacial abnormalities as well as recurrent infections. The neutrophil defect in LAD – II is of the Sialyl-Lewis X glycoprotein (CD 15s), which allows neutrophils to attach to selectins (CD62E) on the endothelial surface. The end result is similar to LAD-I and neutrophils are unable to migrate extravascularly in response to inflammation. Individuals with deficiency suffer from neutrophilia (20,000 – 70,000 cells / $\text{mm}^3$ ) and severe, early onset periodontitis [7, 11].

Oral Manifestations- Page et al studied 5 patients with generalized prepubertal periodontitis and found that all of these patients had abnormalities of all three of the leukocyte receptors, LFA-1, GP 150/95 & Mac-1(CD-11). They stated that this abnormality could account for the observed defect in cell adherence, diminished neutrophil chemotactic response and the enhanced susceptibility to generalized prepubertal periodontitis [5, 7].

Klaldrop, et al. characterized the periodontal conditions of patients with a moderate phenotype of Mac-1, LFA-1 deficiency through examination and gingival biopsy. Their results indicated that these patients suffered from generalized prepubertal periodontitis with an onset during or following the eruption of the primary dentition, rapid horizontal and vertical bone loss, intense fiery red gingiva, marginal gingival proliferation, recession, clefting, bleeding and significant plaque accumulation. Gingival biopsies in these patients showed a marked peripheral blood leukocytosis with minimal or no infiltration of neutrophils into the inflamed extravascular periodontal areas. In contrast, in these heterozygotic patients, they

found invitro, PMN and mono nuclear cell functions that were essentially normal [7].

### **Papillon – Lefevre syndrome (PLS)**

The syndrome is named for the two authors who first detected this condition in 1924. It is a rare autosomal recessive condition with a prevalence of one to three cases per million in the general population. Consanguinity between parents has been reported in atleast one third of the reported cases. It appears equally in males and females. Most reported cases are in Caucasians [14].

The two essential features of PLS is hyperkeratosis of the palms and soles (either diffused or localized) and generalized rapid destruction of periodontal attachment apparatus, resulting in premature loss of both primary and permanent teeth. Other findings such as ectopic calcifications of the falx cerebri and choroid plexus, increased susceptibility to infection, mental retardation and endocrine disorders have been reported [14,15].

A particular form of PLS has been named the “Haim-Munk syndrome”. It is characterized by palmoplantar keratosis and severe early onset periodontitis. This additionally presents digital abnormalities which include osteolysis of phalanges, abnormal length and slender nail of the fingers and toes and a claw like hypertrophic deformity of the nails [15, 16].

### **Chronic granulomatous disease (CGD)**

Patients with CGD have greater occurrence of oral ulcerations and gingival inflammation. Marginal erythema along with extensive attachment loss and gingival recession, significant mobility and furcation involvement has been seen. Bleeding on probing has been reported in few cases. Limited mild periodontitis is consistent with the local factors present [17].

### **Myeloperoxidase deficiency**

Oral manifestations reported in few case reports are deep mucocutaneous candidiasis, palatal candidiasis, rare cases of periodontitis (Generalized Aggressive). But the link has been

not established between myeloperoxidase deficiency and periodontal disease [7].

### **Chediak – Higashi syndrome**

Dental case reports included signs such as dental pain, swollen gingiva with frank purulence, severe horizontal bone loss and lymphadenopathy. Delcourt – Debroyne, et al. examine a 14 year old Chediak – Higashi syndrome patient with severe mobility of teeth, suppuration, severe bone loss and generalized recession with deep probing depths. DNA probe analysis of the bacteria within the periodontal pockets revealed a pathogenic flora consisting of Actinobacillus actinomycetocomitans, P.gingivalis and P.intermedia [18, 19].

### **Periodontal diseases associated with neutrophil disorders**

#### **Localized Juvenile Periodontitis (LJP)**

Accumulation of neutrophils in connective tissues, junctional epithelium and gingival crevice or periodontal pocket of the periodontium is a characteristic morphologic feature of chronic periodontal disease at all stages. When neutrophil function is impaired, there is an increase in periodontal disease as in conditions like Chediak – Higashi syndrome, Localized juvenile periodontitis and other aggressive, early onset periodontal diseases [20].

Localized juvenile periodontitis, formerly termed “Periodontosis”, occurs in adolescents and teenagers. The prevalence of all forms of juvenile periodontitis was reported to be 0.1%. LJP presents characteristic radiographic and clinical signs, including alveolar bone loss most often localized to permanent first molars and incisors, with occasional involvement of other teeth. LJP patients often present with little evidence of surface inflammation of the gingivae, although other gingival inflammation is sometimes seen, and histopathologic studies showed marked inflammatory cell infiltration. Very little or no calculus is formed on the surface associated with these lesions. Loe, et al. in a longitudinal study of the natural history of periodontal disease found that loss of periodontal

attachment occurred slowly in some individuals and rapidly in others [20].

Considerable progress has been made in identifying the microorganisms associated with localized juvenile periodontitis, and much is known about their virulence. Prominent organisms in the subgingival flora of the periodontal lesions include Gram negative facultative anaerobic rods, mainly *Aggregatibacter actinomycetocomitans* and *Capnocytophago* species. Most evidence strongly incriminates *A. actinomycetocomitans* as the cause of LJP [20, 21].

Studies reveal that Gram negative bacteria inhibit neutrophil chemotaxis, suggesting virulence. The mechanism of the chemotaxis defect is one that is intrinsic to the cell and is not reversible by treatment. Familial aggregation of individuals with the defect is seen. The functional suppression of chemotaxis associated with a decrease in the number of receptors for the chemotactic factors FMLP and C5a with no change in receptor affinity monoclonal antibodies to the glycoprotein GP110, were found, which inhibits chemotaxis of normal cells [20].

Suzuki and co-workers, Kumar and co-workers found that the bactericidal activity of LJP neutrophils was depressed. They found the phagocytosis and intercellular killing of neutrophils to be abnormal. Singh reported a marked reduction in the number of neutrophils accumulating in the gingival sulcus in LJP. Other functions including O<sub>2</sub> consumption, superoxide release, ATP energy utilization,  $\beta$ -glucuronidase and lysozyme release have been found to be normal. Recent studies have focused on the transduction mechanism of neutrophils. It was found that the intracellular transduction mechanisms that follow receptor ligand coupling on the neutrophil surface are not clearly established. The putative effectors for the chemotactic receptors of neutrophils are phospholipase C, protein kinase C, methyl transferase or adenylatecyclase. Research has

suggested that an abnormality of signal transduction in LJP patients, presumably at the level of phospholipase, might be due to normal membrane calcium release [20, 21].

LJP is known to appear in 2 forms, LJP-1 (classic form) and LJP-2. LJP-1 is characterized by a decrease in chemotactic responses to a variety of chemotactic factors. This defect has been described as a “pain – receptor defect” because all chemotaxin receptors appear to be decreased. The second form of LJP, clubbed LJP-2, manifests as clinical lesions identical to those seen in LJP -1, however neither decreased chemotaxis, FMLP or C5a receptors nor GP110 is observed in laboratory studies of patient neutrophils [6].

The reason that LJP is limited to certain sites is unknown. However, it has been proposed that the site limitation is a result of a time – dependent “window of opportunity”. Antibody is absolutely required for the opsonization of *A. actinomycetocomitans*. This indicates that antibody responses must be initiated before neutrophils can kill this microbe. The time required producing antibodies of the proper isotype, specificity and affinity may be prolonged by immunosuppressive factor elaborated by the microbe and represents a potential “window of opportunity” during which time the organism may be able to considerable local tissue changes [21].

### **Rapidly Progressive Periodontitis (RPP)**

RPP is a severe form of periodontal disease affecting young adults and/or postpubescent individuals. Individuals with RAP (Rapidly progressive Adult Periodontitis) have a mean age of about 40 years (20-62). Generalized juvenile periodontitis has been associated with plaque and calculus, which suggests a somewhat different microbial etiology than LJP [22].

Neutrophils from such individuals appear to exhibit chemotaxis disorders and no alteration in GP110. The chemotaxis disorders may result from some other phagocyte problem. Kishimoto

has reported that serum from non-diseased individuals did not support phagocytosis of *A.actinomycetocomitans*. RPP probably represents a mixture of several diseases including rapidly progressive adult periodontitis (RAP) [23].

In one of the studies it was found that in 3 of the 19 cases studied (16%), intrinsic defects in leukotaxis could be observed. On the other hand, 6 of 19 cases (32%) exhibited factors in the serum that impaired leukocyte function. Some of these factors were immunoglobulins that functioned as cell directed inhibitors (CDIS) of chemotaxis rather than as autoantibodies. The difference between a CDI and an autosomal antibody is that CDI functions via its Fc region rather than its Fab region by an unexplained mechanism. In one case an elevated factor in serum led to inactivation of the chemotaxin known as chemotactic factor inactivator (CFI) is observed. Extrinsic and intrinsic defects in cell function were not observed in 53% of the cases [22].

### **Aggressive Periodontitis**

A primary characteristic of aggressive periodontitis that differentiates it from chronic periodontitis is the rapid progression of attachment and bone loss. Other consistent features of patients with aggressive periodontitis are that they are otherwise healthy and that the disease demonstrates a familial pattern of occurrence. A number of features are generally but not universally associated with aggressive periodontitis. These include inconsistencies between the amount of microbicidal deposits and the severity of periodontal destruction, the presence of elevated levels of *A.actinomycetocomitans*; and evidence of phagocyte abnormalities and hyper – responsive monocytes/macrophages leading to elevations in PGE<sub>2</sub> and 1 $\alpha$  - 1 $\beta$ . Furthermore, the disease process is self - limiting in some cases of aggressive periodontitis [23, 24].

Some immune defects have been implicated in the pathogenesis of aggressive periodontitis. The

human leukocyte antigens (HLAS), which regulate immune responses, have been evaluated as candidate markers for aggressive periodontitis. HLA A9 and B15 antigens are constantly associated with aggressive periodontitis [24, 25].

Several investigations have shown that patients with aggressive periodontitis display functional defects of PMNs, monocytes or both. These defects can impair either the chemotactic attraction of PMNs to the site of infection or their ability to phagocytose and kill microorganisms. Current studies have also demonstrated a hyper responsiveness of monocytes from LAP patients involving their PGE<sub>2</sub> in response to LPs. This hyper responsiveness may lead to increased connective tissue or bone loss (caused by excessive production of catabolic factors). These PMN and monocytes defects may be induced by the bacterial infection or may be genetic in origin [24].

### **Conclusion**

In summary, it can be seen that neutrophil disorders that either primary or secondary to systemic disease are often associated with severe periodontal disease. Hence neutrophil dysfunction is a risk factor for periodontitis, most likely lowering the host's resistance to periodontal infection by periodontal organisms.

Identifying and understanding the intricacies of the pathogenesis of periodontal diseases associated with neutrophil disorders is highly essential to enable new treatment paradigms and prevention strategies to be developed.

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