Periodontal Disease in Immunodeficient Patients: Clinical Guidelines for Diagnosis and Management

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Abstract

Primary immunodeficiency diseases are rare hereditary conditions that usually occur at a young age; however, secondary immunodeficiency is acquired due to disease, drug treatment and is increasing in frequency among the population. Although periodontal diseases related to these conditions are secondary to other life threatening manifestations, they are very common and easily detectable by the patient, patient guardians and periodontists. Periodontists have a major role in both helping to detect undiagnosed diseases, as well as improving the oral care of diagnosed patients, thus a thorough knowledge of these conditions, causes, local and systemic involvement, diagnostic tools and proper management is very important. This article summarizes selected primary and secondary immunodeficiency conditions such as neutropenia, leukocyte adhesion deficiency (LAD) and Chediak-Hegashi syndrome, and places schematic, diagnostic, and management steps that may help periodontists manage unexplained severe periodontal diseases related to immunodeficiency.

Introduction

Immunodeficiency diseases are defects in the immune system in which the host defense mechanism cannot function properly. Primary immunodeficiency is inherited and therefore is caused by a gene defect. However, secondary immunodeficiency conditions are acquired and usually happen due a defect of lymphocyte function as a result of the usage of drugs, irradiation or invasion of pathogens such as HIV virus and measles.[1]

There are many types of diseases caused by primary immunodeficiency, which is a result of a defect in T-cell or B-cell function, antibody deficiency, or loss of phagocyte function and/or number[2], which for the latter these can be included as any deficiency in the adhesion process of neutrophil [3], NADPH oxidase or chemotaxis.[4]

The epidemiology of the diseases differ based on race, gender, ethnic factors and geographic region[4]. It has been estimated that one in 1200 people are affected by primary Immunodeficiency. Due to cancer therapies, usage of immunosuppressant’s and other biological therapies, the occurrence of secondary immunodeficiency is growing. Organ damage is preventable if there is minimal delay in the diagnosis of immunodeficiency[5].

Periodontal disease is an inflammatory state of the gingiva which affects the supporting structure of the teeth.[6, 7]. Periodontal disease is caused by plaque accumulation, and poor dental hygiene[8] leading to inflammation of surrounding tissue[4]. It has been observed that individuals suffering from any types of immunodeficiency diseases may manifest some oral, dental and facial problems[4]which include periodontal diseases, oral lesions and developmental abnormalities. These can be a sign of immunity defect. Therefore, it is crucial for physicians and dentist to be able to recognize these systematic disorders by the oral manifestation, carry out an accurate diagnosis and perform the corresponding treatment[9].

Neutropenia

Neutropenia is defined by a low absolute neutrophil count (ANC) in the blood lasting more than 6 months, which can cause recurrent infections to a patient [10] with varying severity from stomatitis...
and gingivitis, to more severe pneumonia and sepsis. Different forms of neutropenia such as cyclic neutropenia, chronic benign neutropenia and severe congenital neutropenia (Kostmann syndrome) can all cause periodontal disease.[10, 12]

**Chronic benign neutropenia**

Chronic neutropenia is defined by a non-cyclic low count of neutrophils in the blood without a known underlying systemic disease lasting less than 6 months. It is the most common form of neutropenia in infants and children and is usually not inherited. 80-98% of patients tested positive for the anti-neutrophil antibody [13]. Its manifestation is less severe than Kostmann syndrome, includes high incidence of otitis media, upper respiratory infections, lymphadenopathy and pneumonia but may develop into life threatening infections and sepsis.[10]

Oral Manifestations includes severe gingival inflammation, edematous and hyperplastic papilla.[14] may progress into periodontitis [15] leading to severe horizontal bone loss and teeth mobility [16].

Diagnosis is achieved by a persistent ANC 0.5x10^9/l with a normal total white blood cell count due to elevated numbers of lymphocytes and monocytes [17] and confirmed by anti-neutrophil antibody.

**Kostmann Syndrome**

Severe congenital neutropenia (Kostmann Syndrome) is a rare hereditary syndrome characterized by a very low ANC (less than 0.2x10^9/l) [18] due to maturation arrest during myelopoiesis process [4] and increased apoptosis of myeloid progenitor cells in bone marrow.[19]

Initial symptoms can be summarized as recurrent bacterial infections of the skin, mucosa leading to cellulitis, perirectal abscess, stomatitis, meningitis, pneumonia, and sepsis[20]. Long term symptoms are periodontitis, splenomegaly and hepatomegaly, osteoporosis and myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML) [19].

Oral findings are usually more severe than other forms of neutropenia, with recurrent painful ulceration, [21] diffuse gingival inflammation, alveolar bone loss, teeth mobility and loss of both dentition [22].

Persistent ANC less than 0.5x10^9/l is a significant laboratory finding and diagnosis is confirmed with bone marrow aspiration showing an arrest of neutrophil hematopoiesis at the promyelocyte/myelocyte stage.[10]

**Cyclic neutropenia**

Cyclic Neutropenia is characterized by the repetitive occurrence of neutropenia at average of 21 day period and last for approximately 3-6 days[23]. The mutation is passed along in an autosomal dominant manner. It has been observed that this disease is associated with the mutation in ELA2 gene mapped to chromosome 19p13.3 which encodes neutrophil elastase. Mutations in this gene lead to a shortened neutrophil life[24].

It is characterized by fever, mouth ulcers, lymphadenopathy, multiple abscess formation, exhaustion and susceptibility of infection which can be lethal [25-29]. Reduction in the number of polymorph nuclear leukocytes (PMNs) can be associated with rapid and destructive periodontal disease including aphthous-like lesions[10].

The initial oral characterization of patient includes repetitive ulceration showing little evidence of an inflammatory halo[30], severe gingival inflammation and recession[14, 25], which extended from the gingiva into the alveolar mucosa[25]. Recurrent gingival bleeding along with fever was noted as a sign of this disease [25, 31]. Pocket depths exceeded the 6- to 8-mm range[25] with various levels of tooth mobility [31].

Diagnosis requires serial measurements of the ANC (<1,500) daily or at least three times per week for four to six weeks[32]. It has been demonstrated that Granulocyte Colony-Stimulating Factor(GCSF) can be an efficient treatment for neutropenia[33], as it can lead to a 10 fold increase in ANC and result in a higher life expectancy[34].

Dental management is necessary for these patients to control infections.

- Regular dental appointments to check for the accumulation of bacterial plaque.
- Use of chlorhexidine gluconate mouth wash and a light polishing and scaling in some part of the teeth [25, 31].
- Prophylactic antimicrobials.
- Invasive dentistry should be avoided in neutropenic episodes.
- Oral surgeries to be performed only under specific antibacterial (after microbiological testing) and corticosteroid coverage [21]

**LAD**

LAD is a rare, autosomal recessive, primary immunodeficiency syndrome; characterized by impaired phagocytic functions[35]. LAD is classified according to causative gene mutation into 3 types: LAD I, LAD II and LAD III [36-38].
LAD I is caused by mutation in gene ITGB2 which encodes for CD11/CD18 [39, 40] and ultimately decreases the expression of three integrins on leukocyte surfaces CD11a, CD11b and CD11c and preventing the adhesion of neutrophils to endothelial cells [41]. Characterized delayed separation of umbilical cord, major bacterial infections with no pus formation [35] and impaired wound healing [40], the severity of clinical features are directly related to degree of CD18 deficiency and can be divided into severe (less than 1% CD18 expression) and moderate (2.5% to 10% CD18 expression) [42, 43]. Morbidity rate of severe LAD I is high before the age of 5 [44].

In LAD II, different gene mutations cause defects in the specific Golgi GDP-fucose transporter [45, 46] which reduce CD15s (Sialyl-Lewis X) on the leukocyte surface, thus affecting the rolling phase of neutrophil adhesion [35]. This is characterized by mental retardation and less severe infections in adolescence [41]. Less common LAD III, was only reported in 4 patients suffering from bacterial infections [38] and severe bleeding tendency [47], is believed to be caused by general defect in integrin activation [38].

Periodontal involvement starts as gingivitis at a young age, just after primary teeth eruption. Deep pocket formation and extensive bone loss [48, 49] progress until partial or total premature loss of both primary and permanent teeth [35]. Several case reports showed oral ulceration and delayed wound healing in more than 80% of patients [35].

Primarily, blood test of patients with LAD shows leukocytosis (20,000 to 80,000 cells/ml) [40, 50]. Rebuck skin window or Boyden Chamber shows decreased neutrophil migration and is confirmed using flow cytometry which shows CD18 deficiency in LAD I and sialy-Lewis x ligand deficiency in LAD II [51]. Additional histological analysis of gingival biopsy showed abundance of leukocytes in blood vessels and no leukocyte in tissue [52].

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**Figure 1**: Schematic laboratory tests for diagnosis of listed diseases. LAD, Leukocyte adhesion Deficiency. DHR, Dihydrorhodamine. HIES, Hyper immunoglobulin E syndrome. CVID, Common Variable Immunodeficiency.

*International Dental Journal of Student’s Research, April - June 2015;3(2):96-107*
Bone marrow transplant is the treatment of choice for young LAD patients [53, 54]. However, if not possible, several maneuvers to adjust host response can be achieved such as white blood cell transfusion, antibiotics, interferon and allogenic stem cell transplant [55]. Periodontal treatment usually ends with tooth loss [10] however maintaining the teeth is advocated with the goal of improving patients’ physiologic and psychological health by

- Periodic oral prophylaxis [56]
- Prophylactic Antimicrobial
- Fluoride application and diet counseling
- Extraction should be avoided (due to delayed wound healing)

**Chediak-Hegashi Syndrome**

Chediakhigashi is a rare condition which is inherited in an autosomal manner. This disease is usually fatal and appears with the irregularly enormous lysosomal granules in the leukocytes [57, 58]. This disorder is characterized by numerous repetitive bacterial infections, oculocutaneous albinism, susceptibility to bruising, and mucosal bleeding as well as peripheral neuropathy. In addition, patients may show neurologic dysfunction and movement disorders[3]. Furthermore, the accelerated phase of CHS named Hemophagocyticymphohistiocytosis (HLH) can be recognized by cytopenia, fever, bleeding, lymphadenopathy and hepatosplenomegaly [59-61]. This disorder is connected to the fusion of cytoplasmic granules which can take place in the myelopoesies and can lead to the death of myeloid precursors in the marrow and cause neutropenia. Also neutrophils can have a problem in phagocytosis, chemotaxis and killing bacteria[62].

Intraoral examination showed a full mouth plaque score of 85% [63], gingival bleeding and teeth mobility [3, 58], high frequency of periodontal pockets and bone loss at an early age [10, 64, 65], probing showed more than 30% of the sites 5-8mm deep with concomitant recession defects [66].

Blood testing and examination of giant granules within neutrophils, lymphocytes and natural killer cells using nitroblue tetrazolium dye [10] are essential for diagnosis. Bone marrow aspiration and examination of giant eosinophilic or azurophilic cytoplasmic inclusion bodies within the myeloid lineage cells show a positive reaction to peroxidase staining.

People with Chediak-Higashi disorder can be recognized at a young age, and bone marrow transplant can be a positive treatment which can lower the risk of periodontal disease.[3]

It has been noted that continuous periodontal treatments with regular follow up can help patients avoid further infection and reduce gingival inflammation [67]. In addition, Kornmanet et al. described the importance of periodontal therapy in preventing progressive periodontitis [68].

Long-term antibiotic treatment such as amoxicillin[69] is administered to patients with progressive periodontal disease along with metronidazole [70] to help reduce the periodontal probing depth and promote attachment in patients with the milder form of the disease. [67]. However, full mouth extraction is inevitable in patients with severe progressive periodontal disease refractory to treatment.[71]

**Chronic granulomatous Disease**

Chronic granulomatous disease (CGD) is a very rare immune deficiency syndrome perpetuated genetically. CGD can be characterized by the mutation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase component, leading to the failure of neutrophils and macrophages in killing invading pathogens by impairing the respiratory burst.

*CYBB* is a gene responsible for encoding the gp91phox subunit and is reported as the most common site of mutation. Liver abscesses, skin infections, pneumonia, osteomyelitis, as well as cervical or inguinal lymphadenitis can be seen in young patients[72, 73]. Furthermore, infection and sterile hyper inflammation is also present in CGD patient[74].

Management of CDG is based on control of infections. Broad spectrum antibacterial (as cotrimoxazole)[75], antifungal prophylaxis (asitraconazole)[76], interferon-γ has been shown to improve oxidase activity in neutrophils and monocytes of some patients[77], and to reduce infection rates. Bone marrow transplantation is effective and a more predictable treatment [78].

Some case reports show oral difficulties including oral ulcers[79-84] such as multiple buccal mucosal ulcers in direct contact with dental plaque [81], severe gingivitis, periodontitis [79-81], enamel hypoplasia [84], oral candidiasis [85] , granulomatous mucositis in the upper lip[86] and the soft palate [87], geographic tongue[84] and generalized prepubertal periodontitis,[88] loss of attachment and recession of gingival was noted[88]. Variations of oral findings in CGD patients [72, 89, 90], and Neutrophil dysfunction[10, 91] are probably due to immunosuppressive therapy specially steroids [92].

Patients with CGD can be diagnosed through flowcytometry, dihydrorhodamine 123 (DHR) assay[93] and the nitroblue tetrazolium Test [94].

International Dental Journal of Student’s Research, April - June 2015;3(2):96-107
Treatment:
- Regular dental care and frequent follow-up.
- Antibacterial mouth washes.
- Antibiotics such as clavulanic acid and amoxicillin is needed for any dental work and surgery related to bacteremia [95]
- Antimycotic prophylaxis [95]

Hyper Immunoglobulin E Syndrome

HEIS or Jobs syndrome is a rare multisystemic disease causing host immune defects as well as non-immunological manifestations [96]. It presents itself in two forms, the more common autosomal dominant (AD-HEIS) and the less common autosomal recessive (AR-HEIS) [97], both characterized by high level of immunoglobulin E levels in blood, chronic eczema, recurrent skin and lung infections [98] and decreased bone density [99]. Although the etiology of disease is not clear, several studies concluded that immune defects may be due to defective neutrophil chemotaxis, humoral and cellular immune response impairment including T-cell cytokine signal disruption.

Recent gene analysis showed that most AD-HIES have a mutation in gene STAT3 which causes poor maturation and activation of T17 helper cells, however AR-HIES (different clinical picture with no dental abnormalities) may be attributed to different gene mutation, TYK2 gene (Tyrosine Kinase 2), or the DOCK8 gene (Dedicator of Cytokinesis 8) [100]. Oral findings of AD-HIES is very characteristic to retention of primary teeth or “Double-row” dentition which is found in most reported cases (due to persistence of Her twig epithelial root sheath on root surface, thus preventing root resorption causing delayed shedding), severe candidiasis and oral infections, poor oral hygiene and high plaque index, gingivitis but rare progression to periodontitis, except for 2 patients [79, 101] (This data contradicts most immunodeficiency syndromes, which are more likely to cause severe periodontal destruction.)

There is no one laboratory test that confirms HIES, rather a scoring system (fig. 1)-based on all clinical and laboratory tests is used to confirm HIES, therefore diagnosis of HIES is usually difficult. Recently some reported laboratory tests were added to NIH-HIES score, that helps better detect HIES, as very low Th17 CD4 cell count, and the genetic analysis. [102] The presence of retained primary teeth and unerupted permanent teeth resembles other syndromes like Cleidocranial syndrome, Gardner’s Syndrome, and Down syndrome. A differential diagnosis with these syndromes is noted and confirmed by clinical and laboratory tests. [103]

Treatment is based on prophylactic antimicrobials, intravenous immunoglobulin, and bone marrow transplant shows some success but not a full recovery [104], dental management is focused on
- Periodic follow up and oral hygiene assessment.
- Extraction of primary teeth at correct time of shedding to prevent permanent teeth impaction and enhance oral hygiene.
- Antifungal and antibacterial for oral infections
- Orthodontic correction if needed.

Prognosis of gingival healing after extraction is fairly good with no complications and in most patients periodontal health of permanent teeth can be maintained.
Table 1: Grimbacher et al.[105] Scoring System for HIES

<table>
<thead>
<tr>
<th>Clinical and Laboratory Findings</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>10</th>
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<tbody>
<tr>
<td>Skin abscesses</td>
<td>None</td>
<td>1-2</td>
<td>3-4</td>
<td>&gt;4</td>
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<td></td>
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<tr>
<td>Pneumonia (episodes)</td>
<td>None</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>&gt;3</td>
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<tr>
<td>Parenchymal lung anomaly</td>
<td>Absent</td>
<td>Bronchiectasis</td>
<td>Pneumatocele</td>
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<tr>
<td>Retained primary teeth</td>
<td>None</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>&gt;3</td>
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<tr>
<td>Scoliosis</td>
<td>&lt;10°</td>
<td>15-20°</td>
<td>&gt;20°</td>
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<tr>
<td>Fractures with minor trauma</td>
<td>None</td>
<td>1-2</td>
<td>&gt;2</td>
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<tr>
<td>Highest eosinophil count (cells/L)</td>
<td>&lt;700</td>
<td>700-800</td>
<td>&gt;800</td>
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<td>Characteristic face</td>
<td>Absent</td>
<td>Mild</td>
<td>Present</td>
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<tr>
<td>Midline anomaly</td>
<td>Absent</td>
<td>Present</td>
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<tr>
<td>Eczema</td>
<td>Absent</td>
<td>Mild</td>
<td>Moderate</td>
<td>Sever</td>
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<td>Upper respiratory infections/year</td>
<td>1-2</td>
<td>3</td>
<td>4-6</td>
<td>&gt;6</td>
<td></td>
<td></td>
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<tr>
<td>Candidiasis</td>
<td>None</td>
<td>Oral</td>
<td>Finger Nails</td>
<td>Systemic</td>
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<td>Fatal infection</td>
<td>Absent</td>
<td>Present</td>
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<tr>
<td>Hyperextensibility</td>
<td>Absent</td>
<td>Present</td>
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<tr>
<td>Lymphoma</td>
<td>Absent</td>
<td>Present</td>
<td>Present</td>
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<tr>
<td>High palate</td>
<td>Absent</td>
<td>Present</td>
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Common Variable Immunodeficiency

Common variable immunodeficiency (CVID) is a common heterogeneous primary immune deficiency. Patients with CVID have a deficiency in humoral immunity leading to a defective antibody response, causing repetitive infections of the gastrointestinal and upper respiratory tracts, and susceptibility to some cancers such as lymphoma and autoimmune diseases. Hypogammaglobulinemia has also been seen in these patients. Although normal B-cell numbers have been identified in lymphoid tissue and peripheral blood of patients, it has been noted that B-cells of these individuals have difficulty in differentiating into immunoglobulin-secreting plasma cells. Furthermore, it should be mentioned that the deficiency in monocyte and macrophage function has also been recognized. In addition, in some CVID patients, T-cell malfunction has been identified with decreased CD4 lymphocytes and T-cell receptors, loss of antigen-specific and quick death of T-cells.[4]

Individual suffering from CVID have been diagnosed by having a low level of IgG and IgA[106]. Mutations in a group of genes asTNFRSF13B gene[107], involved in B-cells result in having a defective immunity in CVID[108].

Clinical examinations show dental problems such as gingivitis and lichenoid lesions with Wickham striae,[109] necrotizing ulcerative periodontitis (NUP) [109, 110], severe periodontitis and gingival pain along with bleeding and tooth mobility was demonstrated in a case report.[110]

In order to treat CVID, the primary method used is to replace the antibody by an intravenous or subcutaneous means. This occurs in doses of 400-600mg of antibody per kilogram of the patient’s weight per month.[111]

Dental management as reported in some case reports include:

- Regular oral prophylaxis with crown polishing [109]
- Chlorhexidine digluconate rinse is recommended twice a day.
- Antibiotic therapy [109, 110] such as Amoxycillin and clavulanic acid[109]

Acquired immunodeficiency syndrome

Acquired immunodeficiency syndrome(AIDS) is a disease caused by a human immunodeficiency virus. In this condition HIV targets and attacks T helper cells(CD4) resulting in immune response suppression, the disability of the body’s response to the invading pathogen, predisposes the patient to neurological problems, opportunistic infections, malignancies and oral manifestation [112].

HIV advancement can be detect by monitoring the HIV viral load and T helper cells(CD4+) count, however, it should be noted that there are some common oral manifestations associated with HIV positive patients. Therefore, it can be a useful indicator for screening the immune condition of potential HIV positive individuals and can be easily recognized and detected by clinicians.[113-116] It has been estimated that 70-90% of individual suffering from HIV manifest oral lesions during their phase of the disease [117-119]. Individuals with oral manifestations have less CD4+ than ones without, and it has been observed that there is a correlation between oral candidiasis and a decrease in the CD4+ count(less than 200 cells/mm3).[120]

Some of the important oral manifestation and Lesions present in HIV positive patients are:

- Oral candidiasis (most common oral lesion) [113, 121-123] which are divided in to three groups:pseudomembranous candidiasis, erythematous candidiasis and angular cheilitis[114]
- Oral hairy leukoplakia [114].
- ulcerative disease such as herpes simplex virus, Aphthous ulcerations[114, 124], Neutropenic ulceration [124]
- linear gingival erythema[120, 124]
- oral warts-human papilloma virus[124]
- Necrotizing Ulcerative gingivitis and Periodontitis[NUG/NUP][124, 125]

The follow up appointments are needed for dental care such as scaling and root planning. A 10% povidone-iodine lavage or 0 .12% chlorhexidine gluconate can be used for the elimination of dental plaque and necrotic soft tissue. Utilizing antibiotics such as clindamycin, metronidazole 500g and amoxicillin can be helpful for the treatment. It is crucial to establish proper nutrition in order to reduce potential issues in the oral cavity that can be produced by poor nutrition, as well as manage the patient’s pain.[124]

Leukemia

Leukemia is a type of a cancer caused by an uncontrolled differentiation and proliferation of blood cell precursors resulting in the production of immature cells. Clinically, leukemia is classified into two types: chronic and acute, with the acute phase possibly being fatal. In addition, according to histogenicity, leukemia is divided in to lymphocytic or myelocytic depending on the origin of the cells[126-128]. Acute myeloid leukemia(AML) is more common in adults and acute lymphoid leukemia (ALL) is mostly seen in children[128-130]. Acute myeloblastic leukemia (AML) is characterized by symptoms of...
pancytopenia including fatigue, weaknesses, infection, gingival bleeding, ecchymoses, menorrhagia, and epistaxis [131, 132]. The direct penetration of leukemic cells in lymph nodes, spleen, central nervous system and gingival has been reported [126, 129, 133-135]. Oral complication can be observed in all types of leukemia[136]. Individuals having leukemia are suffering from extreme enlargement of the gingiva along with bleeding[127, 135-139], bulbous enlargement in the interdental papillae [126, 127] a pale blue gum with glazed texture and loss of stippling is one the symptoms of leukemia[126, 127], generalized horizontal bone loss was reported[127] however in some cases bone loss is not recognized[126]. Ulceration and petechiae was noted as a frequent sign[135]. In patient with acute monocytic leukemia and acute myelomonocytic leukemia, gingival infiltration of leukemic cells are commonly seen[140].

Diagnosis by complete blood count peripheral blood smear, shows the presence of blast cells and reveals the type and quantity of white blood cells[126], and flow cytometry of peripheral blood are used for leukemia diagnosis[126, 127], biopsy such as bone marrow aspiration also can be used to confirm diagnosis and type of leukemia[126, 127, 135]

Regular oral prophylaxis is needed. Antibacterials can be used in conjunction with scaling and sub gingival debridement to lower the risk of dental infection during the chemotherapy. Tooth extraction of hopeless teeth can eliminate the infection.[141]

**Conclusion**

Managing periodontal disease of immunodeficient patients is essential for improvement of their physical and psychological health, thus knowledge of these conditions, diagnostic methods and management options is crucial for every dentist. Diagnosis of these diseases is challenging however some clues: may guide the clinician towards a definitive diagnosis, so it is important that precise steps of history taking (medical, familial and dental), clinical examination (extra and intra oral) and laboratory investigations are followed to achieve a successful diagnosis.

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