

## Periodontal Involvement in Leukocyte Adhesion Deficiency: Review of the Literature and a Case Report

Nasim Seyfi<sup>\*1</sup> Mehrnoosh Sabzeghabaie<sup>2</sup> Sara Dehghankhalili<sup>3</sup>

<sup>1</sup>Dept. of Pedodontics, Dental School, Golestan University of Medical Sciences, Gorgan, Iran.

<sup>2</sup>Periodontist, Tehran, Iran.

<sup>3</sup>Dept. of Pediatric Dentistry, AJA University of Medical Sciences, Tehran, Iran.

### Abstract

**Objective:** Leukocyte adhesion deficiency (LAD) is a rare, autosomal recessive inherited disorder; LAD-I which is the most common type, occurs due to mutations in the CD18 gene. This mutation down-regulates the expression of  $\beta 2$  integrin leukocyte cell surface molecules, which are necessary for the adhesion of leukocytes to endothelial cells, transendothelial migration, and chemotaxis. The major symptoms are recurrent severe bacterial infections without pus formation, recurrent or progressive necrotizing soft tissue infections, marked leukocytosis and severe progressive periodontitis accompanied by alveolar bone loss, periodontal pockets, and partial or total early loss of primary and permanent teeth.

**Cases:** Herein, we report a case of moderate LAD-I in a nine year-old boy with severe alveolar bone loss and aggressive periodontitis. For several years, approximately every month, the patient was followed up to evaluate the status of primary and permanent dentition. During these visits, scaling and root planing were performed and severely mobile teeth were extracted. The patient is now under regular follow up.

**Conclusion:** This case confirms the need for interactions between the medical groups to identify and manage medically compromised children with rare diseases. It is important to include LAD in the differential diagnoses of children presenting with periodontal disease. Early correct diagnosis of LAD has various benefits for patients.

**Key words:** Diagnosis, Leukocyte adhesion deficiency syndrome, Periodontitis.

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\*Corresponding Author:  
Seyfi N.  
E-mail:  
drnasimseyfi@gmail.com

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### Introduction

Several hematologic and genetic disorders are related to the development of periodontitis. A large number of reports are available on the effects of systemic conditions on the periodontium; however, a limited number of them have investigated the exact mechanism of the effect of such disorders on periodontal tissues (1, 2). It has been assumed that the main effect of these disorders is mediated by the alterations in host defense mechanisms, which have been clearly explained for some disorders, including neutropenia and LAD, but are less

understood for multifaceted syndromes. Many of such disorders clinically manifest at an early age and may be misdiagnosed as aggressive forms of periodontitis with rapid attachment loss and the potential for early tooth loss. Periodontitis as a manifestation of a systemic disease refers to cases of periodontitis not caused by local factors such as high amount of dental plaque or calculus (3). In 1987, the term LAD was coined by Anderson and Springer and they described the clinical spectrum of this condition (4). Leukocyte adhesion deficiency is a rare, autosomal recessive inherited disorder affecting one/1,000,000 individuals. In general, there are three types

of LADs (5): LAD-I, which is the most common type, occurs due to mutations in a region of the CD18 gene on chromosome 21q22.3 (6, 7). The integrins are cell membrane receptors and include  $\alpha$  and  $\beta$  subunits, which mediate adhesion in all body tissues (8). This mutation leads to absence or severe reduction of expression of  $\beta 2$  integrin molecules on leukocyte cell surface, which are necessary for adhesion of leukocytes to endothelial cells, transendothelial migration, and chemotaxis (6, 9). The major symptoms of the syndrome include delayed separation of the umbilical cord, recurrent severe bacterial infections without pus formation, recurrent or progressive necrotizing soft tissue infections, marked leukocytosis (especially increase of neutrophils), and severe periodontitis with early loss of primary teeth followed by the early loss of permanent teeth (10). Patients with LAD-II show a deficiency in fucosylation of different cell surface glycoproteins, some of which act as ligands for selectins. Consequently, the initial “rolling” of the leukocytes, which is mediated by a reversible contact between L-selectins on the leukocytes and E- or P-selectins on the endothelial cells with their respective sialylated fucosyl ligands on the opposite cells, is disturbed (10). The LAD-II is a disease characterized by impaired fucosylation, recurrent infections, persistent leukocytosis and severe mental and growth retardations (5, 11). The LAD-III syndrome is also quite rare and is characterized by the immunodeficiency of LAD-I and serious bleeding disorders (6). In this type of syndrome, the adhesive ability of  $\beta 1$ ,  $\beta 2$ , and  $\beta 3$  integrins is impaired and, as a result, the patients suffer from recurrent infections in addition to severe bleeding (2, 5). This

syndrome is characterized by pus-free tissue infections and massive hyperleukocytosis ( $>30,000/\mu\text{L}$ ) and is diagnosed by immunofluorescence and functional assays for detecting  $\beta 2$  integrin (7). Overall, various treatments are listed for these patients. Hematopoietic stem cell transplantation, which has a quite high success rate, is considered as the gold standard for this condition (6). In severely ill patients with refractory infections, allogeneic granulocyte transfusion has been beneficial as well. Despite the risk of graft-versus-host disease, allogeneic bone marrow transplantation has been reported to be successful in treatment of this disorder (12). Mobile teeth may be extracted. In case of early alveolar bone loss, generalized mobility will occur and the clinician should examine and suggest the extraction of highly mobile teeth, which cause recurrent infections (6). It is also necessary to do patient follow up in order to ensure adequate oral health. Nonetheless, retroviral mediated gene replacement therapy might be one of the future treatment strategies for this syndrome. This approach may be highly useful for LAD-I since it is a monogenic disorder involving hematopoiesis, and even a minor correction would lead to clinical benefits (13). Herein, we report a case of moderate LAD-I in a nine year-old boy with severe alveolar bone loss and aggressive periodontitis.

## Cases

The patient was a nine year-old boy, first visited at the Department of Pediatric Dentistry, Shiraz University of Medical Sciences, Shiraz, Iran at the age of five and a half years. His parents reported early loss of

primary dentition and gingival problems. The patient was hospitalized at the age of nine months for five days because of high fever and was diagnosed with LAD mainly based on developing bedsores after a short time. According to the laboratory test results showing low level of CD11 and CD 18, and the parents' consanguineous marriage (they were first –degree cousins), the diagnosis of moderate LAD-I was made. Multiple skin scars particularly on the elbows showing previous skin abscesses and infections were also detected (Figure 1). Moreover, oral examination revealed tooth mobility and inflammation of the gums. Furthermore, early loss of most primary teeth was noted along with primary canines and molars with grade II and III mobility (Figure 2). The permanent first molars were erupted with less than two-thirds of their roots being formed. Panoramic radiograph showed severe alveolar bone loss and aggressive periodontitis (Figure 3). The bleeding index was 100%. Periodontal pockets of maxillary and mandibular molars were 5 and 7mm, respectively. The clinical attachment loss in mandibular molars was 9 mm.



**Figure1-Skin scar**



**Figure 2,3- linical and Panoramic views show severe alveolar bone loss and aggressive periodontitis.**

To prevent caries, the clinician performed professional oral prophylaxis, fluoride therapy, and fissure sealant therapy of the first permanent molars at the age of seven.

The parents were then advised to provide oral hygiene, including brushing his teeth with Paradontax dentifrice (Glaxosmithkline, London, England) twice daily; antiseptic mouth rinse (10% povidone-iodine; RazianeSabz, Tehran, Iran) was also prescribed. However, owing to the patient's refusal to use the mouth rinse, Irsha (Donyaye Behdasht, Tehran, Iran) was later prescribed. For skin ulcers, antibiotics, such as clindamycin (300 mg q6h; Kosar Pharmaceuticals, Tehran, Iran) were prescribed. One day before the dental treatments, ampicillin (125mg/5mL q6h suspension; Kosar Pharmaceuticals, Tehran, Iran) and metronidazole (125mg/5mL suspension q8h; Alborzdarou, Tehran, Iran) were administered as prophylaxis and continued for the next four days.

For several years, approximately every month, the patient was visited at the Department of Pediatric Dentistry to evaluate the status of the primary and permanent dentition (Figure 4). During the follow-up visits, scaling and root planing was performed. In addition, the patient's severely mobile primary mandibular canines and primary right lateral incisor were extracted. Six months later, upper primary canines with mobility grade III at the age of seven were extracted. Anterior mandibular teeth showed gingival inflammation in the next follow up session. Since the patient had pain during plaque control, using a topical anesthetic gel (20% benzocaine) before tooth brushing was recommended. Monthly follow up examinations were affected by the patient's hospitalizations because of skin abscesses. Recently, the mobile mandibular right first permanent molar was extracted after taking antibiotics since it was severely mobile and had a periapical abscess.



**Figure4-Clinical view in follow up visit**

At present, the patient is under regular follow up. Due to his improved condition in the recent years, bone marrow transplantation has not yet been considered and follow ups should be continued.

## Discussion

The LAD-I is a rare, inherited, autosomal recessive, immunodeficiency disorder resulting from the combined absence of expression of leukocyte integrins LFA-1, Mac-1, and p150, 95 on the surface of leukocytes (6). This type of LAD affects one per 1,000,000 individuals and usually occurs during infancy or early childhood with severe recurrent bacterial infections, lack of pus formation, and impaired wound healing (14). The primarily involved areas include the skin, oral mucosa and gastrointestinal tract (5). The disease is categorized into two groups of severe (<1% expression of CD18) and moderate (1–30% expression of CD18) phenotypes according to the degree of expression of CD18 (6). The patients with moderate phenotype are usually diagnosed late. Because of extensive necrotizing bacterial infections, the more severe phenotype usually leads to mortality before the age of two. On the other hand, the patients with moderate phenotype live a longer life with 75% dying before the age of 38. The quality of life of such patients is usually poor and involves recurrent viral and bacterial infections, including periodontitis,

necrotic skin lesions, and ulcers in the gastrointestinal tract (5).

In general, recurrent oral ulcers are commonly found in this syndrome. In spite of preventive therapy, rapidly progressive juvenile periodontitis is prevalent due to the severity of the disease (15). Progressive periodontal disease in children with LAD-1 may result in severe systemic infections and death; thus, early diagnosis with proper intervention is critical to improve the prognosis. Furthermore, in case of inflammation, active process of tooth eruption may be affected (8, 11). The most common pathogens causing infection in LAD include *Staphylococcus aureus*, *Pseudomonas* spp., gram-negative enteric species and *Candida albicans* (5). Oral candidiasis is also a frequently observed complication, which must be treated promptly (16). Considering the chronicity of the disease and risk of serious complications, patients suffering from LAD may have numerous hospital admissions and long hospitalization periods to receive supportive medical treatments (5). Delayed cord separation may occur in healthy infants, while it is often accompanied by acute omphalitis in patients with LAD type I. Overall, cord separation is considered normal or delayed when it takes place after two or three weeks of age, respectively (10). In case no evidence of even the initiation of cord separation from the umbilicus is found after four weeks, LAD should be suspected. Although an association has been reported between delayed umbilical cord separation and leukocyte dysfunction in many cases, it is not always accompanied by leukocyte adhesion (5) and this was not the case in our patient either. Delayed umbilical cord separation is not observed in LAD type II

(13). Because of poor wound healing and defective neutrophil function, gingival health maintenance is difficult for patients; therefore, dental care must be emphasized by a dental care provider for the remaining teeth. Treatment approaches in these patients should include prevention of local (dental) and systemic infections. Defective expression of CD18 results in enhanced susceptibility to bacterial infections (caused by neutrophil dysfunction) and viral diseases since CD18 plays a major role in cytotoxic T cell activity (8). Thus, a combination of wide-spectrum antibiotics, such as trimethoprim-sulfamethoxazole, and acyclovir are used in such cases. Nevertheless, in spite of optimal prophylaxis to prevent systemic infections, oral disease is still a problem in LAD-I patients and requires specific measures, including reinforcement of oral hygiene, prevention of local infections (by using chlorhexidine), and periodontal disease follow up (8). Hematopoietic stem cell transplantation, which has a quite high success rate, is considered as the gold standard treatment for this condition (6). In severely ill patients with refractory infections, allogeneic

granulocyte transfusion has been beneficial as well.

Considering the high prevalence of primary immunodeficiency in the Iranian population (9) as well as the high rate of consanguineous marriage in Iran, more attention should be paid to public education and awareness in this regard. Moreover, since LAD has a genetic etiology, genetic counseling should be provided for the affected children's parents, siblings, and the extended family. Prenatal diagnosis should also be taken into account for the patient's siblings who are at risk of having children with autosomal recessive immunodeficiency (2).

## Conclusion

It is important to include LAD in the differential diagnoses of children presenting with periodontal disease. Early, appropriate diagnosis of LAD provides various benefits for the patients as well as their families and in this context, cooperation between different medical groups is essential.

## Conflict of Interest: "None Declared"

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