Leukocyte Adhesion Deficiency: A Case Report and Review

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ABSTRACT

Leukocyte adhesion deficiency (LAD) is a rare inherited primary immunodeficiency disorder characterized by the presence of a defect of phagocytic function resulting from a lack of leukocyte cell surface expression of β2 integrin molecules (CD11 and CD18) that are essential for leukocyte adhesion to endothelial cells and chemotaxis. A small number of patients with LAD-1 have a milder defect, with residual expression of CD18. These patients tend to survive beyond infancy; they manifest progressive severe periodontitis, leading to partial or total premature loss of the primary and permanent dentitions. Close cooperation with pediatricians and immunologists is often the key to successful management of pediatric patients with LAD. The purpose of this report was to present the case of a 5-year-old boy with moderate leukocyte adhesion deficiency-1 and severe periodontitis, cellulitis and illustrate the need for periodic oral checkups to avoid the progression of oral diseases and prevent premature tooth loss. (J Dent Child 2012;79(2):105-10)

Received December 15, 2010; Last Revision November 6, 2011; Revision Accepted December 14, 2011.

KEYWORDS: SYNDROMOLOGY / CRANIOFACIAL ANOMALIES, PERIODONTICS, ORAL PATHOLOGY

Inflammation is fundamentally a protective response with an ultimate goal of ridding the organism of both the initial cause of cell injury and consequences of such injury: the necrotic cells and tissues. The vascular and cellular responses of inflammation are mediated by chemical factors derived from plasma or cells and triggered by the inflammatory stimulus. The inflammatory process is typified by a series of events due to the presence of an antigen that leads to tethering and rolling of the leukocytes. This is followed by adhesion to the endothelial lining, followed by chemotactic movement toward the antigenic stimulus.[1]

Leukocyte adhesion deficiency (**LAD**) is an autosomal recessive disorder that occurs due to a defect of phagocytic function. LAD is classified into 3 types: LAD I; LAD II; and LADIII. LAD I has been described in more than 300 patients worldwide and LAD II and III in less than 10 children each.

ETIOLOGY

LAD I is due to the mutations in a gene (ITGB2), which is located on chromosome 21 and encodes the β2 subunit of the integrin molecule. LAD I is also the consequence of mutations in the gene coding CD18, the β2 integrin subunit of the hetero dimers LFA-1, Mac-1 (CR3), and p150, 95.[2,3] Since the α subunit will not bind the defective β subunit, almost no CD18 will be expressed on the leukocyte surface membrane. This will eventually lead to severe defects in the firm adhesion of leukocytes on endothelial cells and, thus, lead to a defective inflammatory response that can cause infections.[4] Rarely, CD18 may be present on the leukocyte surface but will remain nonfunctional, due to the mutation.[5] A small number of LAD-1 patients have a milder defect with a residual expression of CD18. These patients tend to survive beyond infancy.[6]

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In LAD II, the genetic defect is located on chromosome 11 with mutations in the gene encoding the specific Golgi GDP-fucose transporter.[7,8] In LAD II, mutations in the gene encoding the fucosyl transporter impede fucose entry in the Golgi apparatus and the fucosylation process normally taking place in the Golgi apparatus. As a consequence, all fucosylated glycoproteins, including the H antigen on erythrocytes and CD15s (Sialyl-Lewis X) on leukocytes, are markedly decreased. Since CD15s is the ligand for the endothelial selectins, the main defect will be in the rolling phase of the adhesion process. The precise mechanism leading to the severe psychological and growth retardation is still unknown.

LAD III involves a general defect in integrin activation. The precise molecular defect in LAD III is still unknown, although it may be the result of several different genes involved in the inside-out signaling for general integrin activation.[9-11] Defects in the activation of β1, β2, and β3 integrin subunits have been observed, and it seems that this rare syndrome may be due to several defects in molecules involved in integrin activation.[12]

CLINICAL DESCRIPTION

In all LAD I patients, the prominent clinical feature is recurrent bacterial infections, primarily localized to skin and mucosal surfaces. Infections are usually apparent from birth onwards, and a common presenting infection is omphalitis with delayed separation of the umbilical cord. The absence of pus formation at the sites of infection is one of LAD I's clinical hallmarks. Severe gingivitis and periodontitis are major features among all patients who survive infancy. Impaired healing of traumatic or surgical wounds is also characteristic of this syndrome.[13]

The severity of clinical infectious complications among LAD I patients appear to be directly related to the degree of CD18 deficiency. Two phenotypes, designated as severe deficiency and moderate deficiency, have been defined. Patients with less than 1% of the normal CD18 surface expression exhibit a severe form of disease with earlier, more frequent, and more serious episodes of infection—often leading to death in infancy. Patients with some surface expression of CD18 (2.5-10%) manifest a moderate to mild phenotype with fewer serious infectious episodes and with survival into adulthood.[2] In vitro studies have demonstrated a marked defect in random migration as well as chemotaxis to various chemo attractant substances. Adhesion and transmigration through endothelial cells were found to be severely impaired.[14]

LAD II-affected children are born after uneventful pregnancies with normal height and weight. No delay in the separation of the umbilical cord is observed. Affected individuals have the rare Bombay (hh) blood phenotype. Later in life, they show severe mental retar dation, short stature, and a distinctive facial appearance. Infections are generally not life-threatening and are usually treated in an outpatient clinic. There is no pus formation at the site of infection. After children turn 3 years old, the frequency of infections decreases and they no longer need prophylacticantibiotics.[15] The hallmark of LAD II syndrome is the deficiency in the expression of the sLex antigen, the selectin ligand, on leukocytes. Neutrophilia (10,000-40,000/mm^3) is a constant finding.[16] LAD II is also called congenital disorder of glycosylation type IIc (CDG IIc) syndrome.

The clinical picture of LAD III in the 4 patients described so far with this syndrome is very similar to LAD I, but also includes defects in platelet activation[17] and a severe bleeding tendency.[18]

DIAGNOSTIC METHODS

A simple complete blood count test is the most important diagnostic test, which should reveal a profound neutrophilia. Fluorescence-activated cell sorter analysis, using specific monoclonal antibodies, is essential for the diagnosis of both LAD I and LAD II. Adhesion assays are not performed in most laboratories and should be conducted only in laboratories which are specialized in these assays.[19]

PRENATAL DIAGNOSIS

As leukocytes express CD18 on their surface from 20 weeks of gestation, cordocentesis can establish the diagnosis.[20] In families where the exact molecular defect has been previously identified, an earlier prenatal diagnosis is possible by chorionic villus biopsy. In LAD II, the Bombay blood phenotype can be checked at 20 weeks of gestation. Genetic analysis of the defective gene can be performed at 10 to 11 weeks of gestation.

MANAGEMENT AND TREATMENT

The most important focus of managing an LAD case should be to control infections, as these patients are extremely prone to both oral and gastrointestinal (GIT) infections. Prompt antibiotic therapy should be initiated as early as possible in case of acute infection. Granulocyte transfusion should be restricted to life-threatening situations when all other measures have failed. Blood transfusion should be given in bleeding episodes in LAD III. In the severe phenotype of LAD I, bone marrow transplantation has been performed and excellent results have been reported.[21] Gene therapy is still experimental in LAD I.[22] In 2 cases of LAD II, fucose supplementation showed encouraging results.[16,23]

The purpose of this report was to present the case of a 5-year-old boy with moderate leukocyte adhesion deficiency-1 and severe periodontitis and cellulitis and to illustrate the need for periodic oral checkups to avoid the progression of oral diseases and prevent premature tooth loss.

CASE REPORT

A 5-year-old boy was referred to the Department of Pedodontics and Preventive Dentistry of M.S. Ramaiah Dental College and Hospital, Bangalore, Karnataka, India with the complaint of right facial swelling observed over the previous week. He was born following an uncomplicated pregnancy at 37 weeks to a couple with family history of consanguineous marriage. The patient had lost 2 elder siblings who passed away at 3 and 2 months old, respectively, due to abdominal distention where the underlying disease could not be diagnosed. A positive history of delayed separation of the umbilical cord was reported.

The patient had a history of repeated hospitalization due to recurrent gastrointestinal tract and oral infections. His medical history revealed that many hospital admissions occurred from birth onward for the recurrent infections. At 2-years-old, the child was diagnosed by an immunologist to be suffering from LAD I, based on clinical and laboratory findings which were supported by the partial absence of CD 18, CD11b, and CD 11c, as determined by flow cytometry. Hematologic investigations revealed neutrophilic leukocytosis with mild microcytic hypochromic anemia. Blood chemistry was normal. He also reported repeated skin infections and delayed wound healing (Figure 1).

Upon facial examination, the patient had extraoral swelling extending from the canine region to the lateral border of the mandible's ramus (Figure 2). His skin was stretched and shiny, with a localized elevation in temperature; however, no draining sinuses or fistulae were observed. Upon intraoral examination, there was generalized mobility of teeth with severe alveolar bone loss affecting all of his primary dentition and all permanent first molars (Figure 3). The child also had proximal dental caries and: grade III mobility in relation to primary maxillary anterior teeth; and grade II mobility of permanent mandibular incisors, permanent first molars, and primary second molars. There was severe loss of attachment and gingival recession in all noted areas (Figures 4-5). The primary second molars also had grade III furcation involvement.

A panoramic radiograph showed moderate to severe bone destruction associated with almost all erupting teeth, especially around permanent first molars (Figure 6). The case was diagnosed as periodontitis associated with LAD I. The patient had severe spontaneous pain in relation to his primary mandibular right second molar, in spite of being on intravenous antibiotic therapy as prescribed by pediatricians. As the swelling had not regressed, the tooth was extracted to provide access for drainage under continued antibiotic cover. The patient was recalled for follow-up after 2weeks, and the extraction site showed moderate healing.

DISCUSSION

LAD I is rare disorder that occurs in 1 in 10 million births.[24] LAD was described first in patients with delayed separation of the umbilical cord, neutrophilia, neutrophil defects, and systemic bacterial and fungal infections.[25] The severity is based on the relative expression

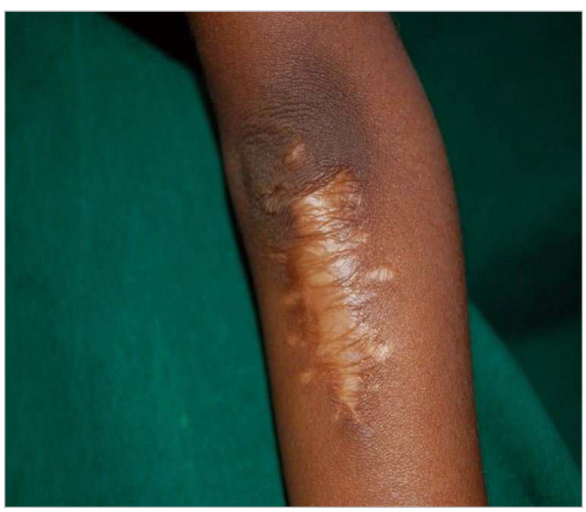

Figure 1. Abnormal wound healing in pediatric patient with LAD type 1.

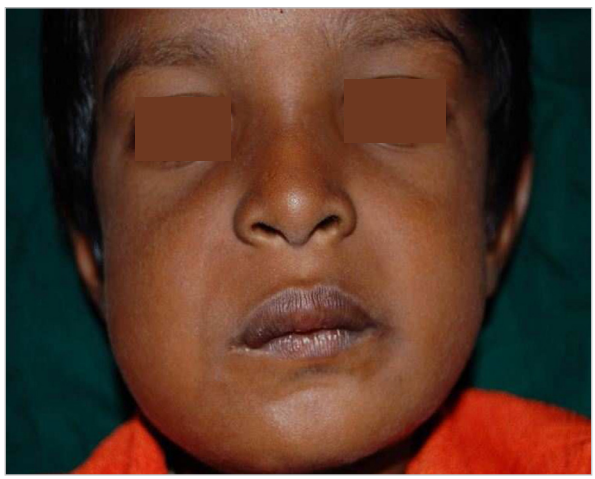

Figure 2. Patient with right facial swelling in pediatric patient with LAD type 1.

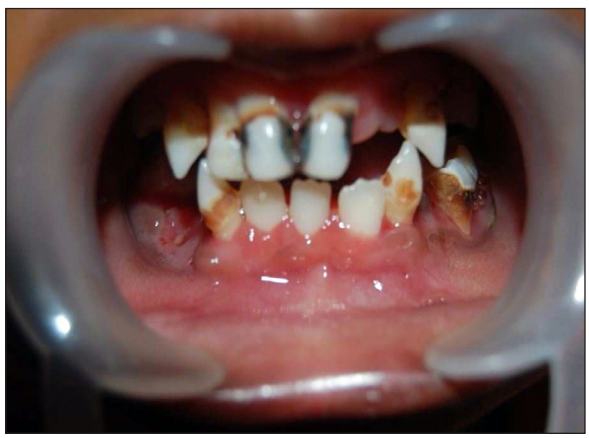

Figure 3. Intraoral findings of patients with leukocyte adhesion deficiency in pediatric patient with LAD type 1.

of CD18, with less than 1% of normal described as severe, whereas 2.5% to 10% of normal is considered moderate to mild.[26]

The patient had a history of recurrent infections, delayed separation of the umbilical cord, and leucocytosis that is consistent with LAD I. A partial absence of neutrophil CD18, CD 11b, and CD 11c confirmed the diagnosis and categorized the case as moderate phenotype.

Waldrop et al.,[27] described the oral conditions in a family suffering from LAD I. The father, who was affected by severe LAD I, experienced delayed healing of huge skin ulcers on his leg. He lost his primary dentition by 3 years old and his permanent dentition by 13 years old.

Movahedi et al.,[28] reported 15 cases of LAD I in Iran over a 14-year period. The patients' ages ranged from 10 months to 14 years old (median=4 years); 10 were male and 5 were female, and 93% of the parents had consanguineous marriages. The most common manifestations were: recurrent infections (~93%); poor wound healing (86%); oral ulceration (86%); and skin abscesses (80%). Regarding periodontal disease, gingivitis was reported in 64% of subjects. Six of 15 patients died, and 2 had a moderate phenotype.

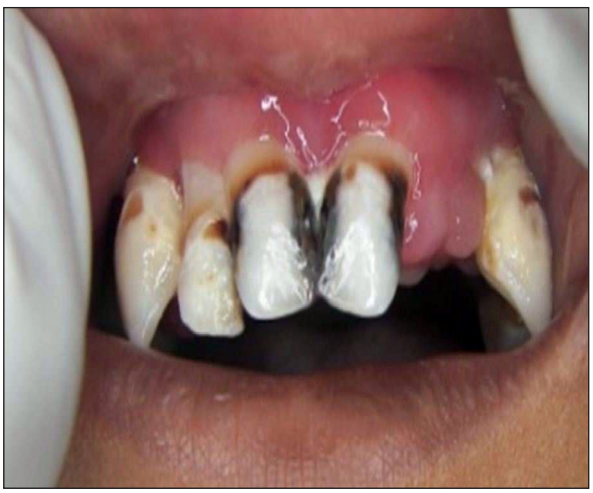

Figure 4. Severe gingival recession of upper anterior region in pediatric patient with LAD type 1.

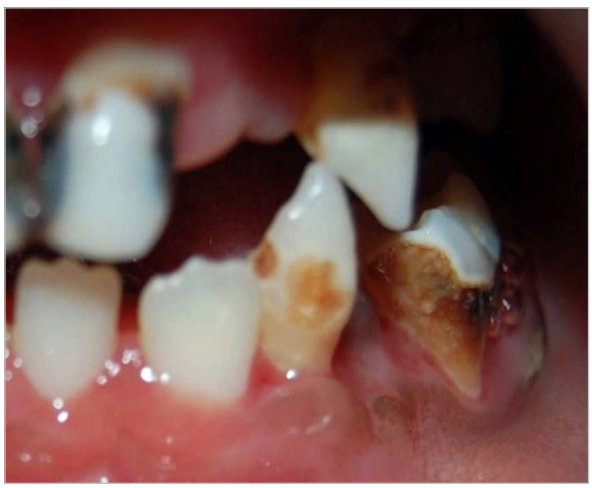

Figure 5. Gingival recession in the posterior region in pediatric patient with LAD type 1.

The intraoral clinical findings in this report are similar to the characteristics of generalized prepubertal periodontitis.[29] These include the: early onset of the disease that affects the primary and permanent dentitions; intense redness and inflammation of the gingiva; and rapid periodontal destruction that seemed refractory to conventional periodontal therapy. Similarly, the clinical and radiographic appearance of our patient resembled generalized juvenile periodontitis (**GJP**).[30] Comparing LAD patients to GJP patients is difficult. LAD involves neutrophils, lymphocytes, and monocytes, while GJP has been associated primarily with only neutrophil defects.[31] Aggressive periodontal disease also has been described in children with a broad range of systemic disorders, such as neutropenia[32] and Papillon Lefevre syndrome.[33]

The importance of maintaining the dentition as long as possible in the child's developing orofacial complex was one of our primary concerns in the initial philosophy of treatment. It was argued, however, that, in spite of the patient's poor wound healing ability, extraction was the treatment of choice to reduce the risk of future infections.

LAD is one of the rare primary immunodeficiency disorders that is often undiagnosed. Additionally, patients suffering from the severe type often succumb to the overwhelming infection before the diagnosis itself. Patients with a moderate form of LAD have increased life expectancy that is again fraught with repeated episodes of infection. These patients have to be viewed as high risk for both periodontitis and dental caries and require an extensive preventive program comprising oral hygiene measures. Fluoride applications/topical application of amorphous calcium phosphate-casein phosphopeptide and diet counseling must be initiated early.

Moreover, any dental procedure in these patients carries the risk of infection and delayed healing and has to be initiated after obtaining the opinions of both a pediatrician and immunologist. Periodic oral checkups

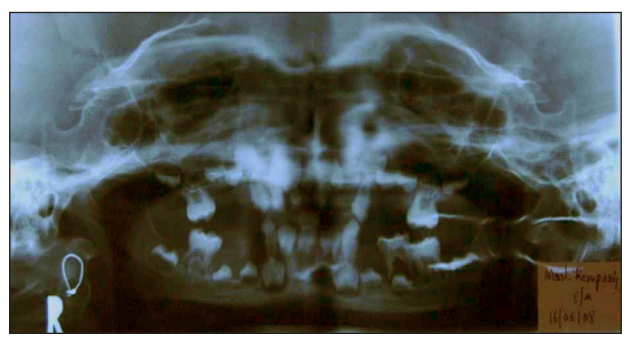

Figure 6. Panoramic radiograph of pediatric patient with LAD type 1 showing generalized alveolar bone loss.

are essential to avoid the progression of oral diseases, and close cooperation with a pediatrician and immunologist is often the key to successful management of a pediatric patient with LAD.

This report emphasizes the importance of the differential diagnosis of severe immunodeficiency disorders in children and adolescents and mandates the importance of combined care by medical and dental practitioners to prevent tooth loss and control oral infections.

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