

Case Report

Osteomyelitis in leukocyte adhesion deficiency type 1 syndrome

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Abstract

Leukocyte adhesion deficiency type 1 (LAD-1) is a rare, inherited immunodeficiency that affects one per million people yearly and usually presents with recurrent, indolent bacterial infections of the skin, mouth, and respiratory tract and impaired pus formation and wound healing. A 13-year-old girl diagnosed LAD-I at the age of 7 years was brought to the Immunology, Asthma and Allergy Research Institute, Tehran University of Medical Sciences, because of a draining plaque on the left leg for 2.5 years. She had recurrent skin infections and had been treated with repeated courses of different antibiotic combinations, with temporary responses, since 5 years of age. Examination revealed a 7 × 8 cm minimally erythematous hyperpigmented plaque with multiple draining sinuses on the left leg. Tissue culture yielded *Pseudomonas aeruginosa*. Flow cytometry showed CD18 (18.79%), CD11a (51.59%), CD11b (18.61%) and CD11c(10.60%). A plain radiography of the left leg revealed osteomyelitis. It is highly suggested that patients diagnosed mild to moderate LAD-1 with recurrent skin infection and simultaneous weak response to conventional therapy undergo (BMT) marrow transplant to prohibit subsequent life-threatening complications.

Key words: leukocyte adhesions deficiency; bone marrow transplantation; osteomyelitis

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Introduction

Leukocyte adhesion deficiency (LAD) is a rare primary immunodeficiency. The clinical picture is characterized by marked leukocytosis and localized bacterial infections that are difficult to detect until they have progressed to an extensive level secondary to lack of leukocyte recruitment. [1,2] There are three types of leukocyte adhesion deficiency syndromes, and the most common of them is leukocyte adhesion deficiency type I.

Leukocyte adhesion deficiency type I (LADI) is an autosomal recessive immunodeficiency syndrome [3]. It is a failure to express CD18 (αMb2 and αLb2), which forms the receptor for C3b with CD11b and is expressed on myeloid and lymphoid cells. Most patients with LAD I do not express CD18 on lymphocytes, macrophages, and neutrophils. These patients succumb to life-threatening infection, usually within two years of life. Some patients have a milder form of LAD I and express approximately 5-10% of the usual CD18 levels on leukocyte cell surfaces. [4] LAD I has been described in more than 300 patients worldwide. [5]

LAD type 1/variant syndrome consists of a moderate LAD type 1-like syndrome and a severe Glanzmann-like bleeding disorder. The clinical picture consists of delayed cord detachment; recurrent bacterial, fungal, and cytomegalovirus organism infection, beginning early in infancy; and poor wound healing. Bleeding tendency is moderate-severe, requiring repeated platelet transfusions. Neutrophilia is not as severe as seen in LAD type 1, with a white blood cell (WBC) count of 10,000-30,000 with 60-90% neutrophils. [5,6] Successful (BMT) marrow transplantation has been performed in patients with LAD type 1/variant syndrome. [7]

Case report

A 13-year-old girl was admitted to the Immunology, Asthma and Allergy Research Institute, Tehran University of Medical Sciences, because of a draining plaque on the left leg for 2.5 years (Figure1). She was the second child of healthy parents, and both the mother's pregnancy and the baby's delivery had been normal. At the age of 13 days, her umbilical

Figure 1. A draining plaque on the left leg at the age of 13 years.

cord detached spontaneously. The patient was diagnosed LAD-I at the age of seven years. A cutaneous infection in the form of pustule on the left thigh had been first noted when she was five years of age (Figure2), which healed spontaneously after 1.5 months. Since then, similar infections had occurred approximately every two years on the same limb. She was treated with repeated courses of different antibiotic combinations including cloxacillin, sulphamethoxazole-trimethoprim, imipenem, ciprofloxacin, vancomycin and amikacin with subsequent partial responses in which neither the size of the cutaneous ulcer nor the severity of the local infection changed prominently. A cutaneous infection on the left thigh at the ages of seven and nine years was successfully treated with skin grafting to close the defect, but after repeated procedures the skin grafts were all rejected (Figure2). The patient had no history of recurrent otitis media, pharyngitis or pneumonitis. She was once treated for periodontitis at the age of seven years. Although she was candidate for a bone marrow transplant when she was diagnosed LAD-I, her parents did not consent to the procedure.

Examination revealed a 7 × 8 cm minimally erythematous hyperpigmented plaque with multiple draining sinuses on the left leg. Tissue for culture yielded *Pseudomonas aeruginosa*. Osteomyelitis was suspected, and a plain radiography of left leg was performed in which the diagnosis of osteomyelitis was confirmed by a radiologist (Figure3).

Laboratory data at admission showed high leukocyte counts (21,300/mm³) associated with neutrophilia (79%). The T- and B- cell lymphocytes and serum immunoglobulin assay were all normal. The flow cytometric analysis of peripheral blood

Figure 2. Scar of necrotizing ulcer after skin graft on the left thigh at the age of 13 years.

neutrophils revealed CD18 (18.79%), CD11a (51.59%), CD11b (18.61%) and CD11c (10.60%), which is indicative of leukocyte adhesion deficiency type I. Liver and kidney functions were normal. Blood culture grew no organisms.

Discussion

LAD affects nearly one out of every million individuals [8]. In this report, we describe the findings of a patient with clinical features of mild to moderate LAD-I disorders. Delay in the umbilical cord detachment is often a leading sign of this disease and may result in serious omphalitis [5].

Our patient did not have any undue problems in the natural separation of the umbilical cord. She was healthy until the age of five years, when the first signs of the disease presented with emerging cutaneous infection on the left thigh, recurrent cutaneous infections in the same limb, and severe periodontitis. In spite of recurrent skin infections, no history of perianal abscess, pneumonia, or chronic discharging otitis media were seen in our patient, which are typical clinical features of moderate to severe LAD-I [9]. In this patient recurrent skin infections progressed to large chronic ulcers that became polymicrobial in character, including anaerobic organisms, in which the very slow healing process required months of antibiotic treatment and plastic surgical grafting which was not successful at times. Finally, because of the chronicity and incurableness of the skin lesions, complicated osteomyelitis resulted, which made the treatment process more sophisticated for this child.

Figure 3. Osteomyelitis on left leg (plain radiography)

Osteomyelitis is less commonly caused by gram-negative organisms, and *Pseudomonas aeruginosa* is unusually offensive even as a secondary invader [10]. Osteomyelitis caused by *Pseudomonas* has usually been associated with surgery [10,11], infections or instrumentation of the genitourinary tract [12,13], and heroin addiction [14,15]. *Pseudomonas* osteomyelitis in the feet of children caused by puncture wounds was first reported 1986 [16], and similar reports have appeared in literature since then [17,18].

According to our searches in the medical literature, no patients with LAD-I similar to the clinical presentation of this case has been reported yet. Patients with some surface expression of CD18 (2.5-10%) manifest a moderate to mild phenotype with fewer serious skin, mucosal and respiratory tract infections, and will survive into adulthood [19]. In our patient, the recurrent skin infections in one limb and mild periodontitis without any respiratory tract involvement until 13 years of age portray a rare presentation of this disorder. In other words, we may call it a mild form of LAD-I because the only leading sign in LAD-I is the recurrent skin infections.

Patients with severe or moderate to mild forms of LAD-I benefit from daily trimethoprim-sulfamethoxazole prophylaxis and from broad-

spectrum antibiotic therapy if and when infection occurs. Regular culture swabs or biopsy is very important for the determination of the etiologic agent, and sometimes very prolonged antibiotic treatment is essential for indolent infections [20,21]. Bone marrow and stem cell transplantation are current options in treatment [22].

Conclusion

Pediatricians must keep in mind the possibility of LAD-I when faced with a child with recurrent skin infections and no proper response to antibiotic therapy. Suspicious cases should be referred to immunology centres for further evaluations.

It is highly recommended that patients diagnosed with mild to moderate LAD-I with recurrent skin infections and simultaneous weak responses to conventional therapy undergo BMT to prohibit subsequent life-threatening complications.

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