

Case Report

Leukocyte Adhesion Deficiency Type 1 Presenting as Leukemoid Reaction

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ABSTRACT

The hallmarks of leukocyte adhesion deficiency (LAD) are defects in the leukocyte adhesion process, marked leukocytosis and recurrent infections. These molecular and clinical manifestations result from an impaired step in the inflammatory process, namely, the emigration of leukocytes from the blood vessels to sites of infection, which requires adhesion of leukocytes to the endothelium. Over last 20 years, three distinctive defects in the leukocyte adhesion cascade, involving several precise ordered steps such as rolling, integrin activation and firm adhesion of the leukocytes have been described. While LAD I and II are clearly autosomal recessive disorders, the mode of inheritance of LAD III is still not clear. LAD I is due to structural defects in the integrin molecule, preventing firm adhesion to occur. We present a case of a male neonate referred with continuation of leukemoid reaction and multiple non healing ulcers, gingivitis and periodontitis in spite of good antibiotic therapy.

Keywords: Leukocyte Adhesion Deficiency Syndrome; Leukemoid Reaction; Neonate

Introduction

Classically leukocyte adhesion deficiency (LAD) is due to three distinctive defects in the adhesion cascade (1) and plays a major role in the recruitment of leukocytes to the

site of inflammation. The mode of inheritance of LAD I/variant or LAD III is not clear, while LAD I & II are autosomal recessive disorders. LAD I is reported more than other types of LAD, which affects about one per 10 million individuals. Only

Received : 8 July 2012

Accepted : 31 february 2013

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300 cases of LAD I have been reported worldwide (2, 3). LAD I is the consequence of mutations in the gene coding CD18, the $\beta 2$ integrin subunit of the heterodimers LFA-1, Mac-1 (CR3) and p150,95(4, 5).

Clinically these patients present as recurrent bacterial infections of skin and mucosal surfaces. These infections are apparent from birth like omphalitis with delayed separation of the umbilical cord. However pus formation is conspicuously absent from the site of infection. Later on, these patients may have infections involving gums which may progress to involve the jaw bone also (6).

Case Report

A 13 day old male neonate presented to emergency with chief complaints of fever since last 10 days, abdominal distension and excessive cry since last 3 days. The patient was an otherwise healthy newborn, born vaginally at 38 weeks of gestation, weighed 3.2 kg and no significant history of illness in mother or adverse antenatal events. He was taking antibiotics from practitioner on outpatient basis in form of intramuscular injections. He was passing adequate urine and stools.

At admission, the patient was febrile (axillary temperature of 102 °F) and had tachycardia (HR=200 bpm). He looked pale and had excessive cry with abdominal distension. Bowel sounds were present. He also had signs of periomphalitis with the umbilicus indurated and edematous, surrounded with a hyper pigmented patch, 1 by 0.5 cm in size, and with no discharge (Fig. 1). He had multiple ulcers (largest being 4 by 2 cm) over the chest, back and chin with eschar formation and no pus discharge with intact umbilical cord (Fig. 2). No significant lymph node enlargement was detected, and no sign of organomegaly was found in abdominal examination. Oral cavity revealed severe gingivitis and periodontitis (Fig 3).



Fig. 1- Periomphalitis with ulcer over chest wall



Fig. 2- Persisting ulcer with no pus formation in spite of antibiotic coverage



Fig. 3- Periodontitis with gingivitis

Regarding our first impression of facing a neonatal sepsis, further investigations were performed which revealed a total leukocyte count of 42,000/mm³ with an absolute neutrophil count of 34,400/mm³ which was much higher than the normal ranges mentioned in the Monroe's charts for neonates at 320 hr of life, RBC count of 3.40

million/mm³, with a haemoglobin concentration of 12.3 mg/dl, haematocrit of 37.1% and a platelet count of 50,000/mm³. The differential leukocyte count was polymorphs 82%, lymphocytes 17% and eosinophils 1%.

Pathologist remarked on general blood picture as leukemoid reaction with smear showing predominantly mature segmented cells of granulocyte series including myelocytes, meta myelocytes and band forms. Polymorphs also showed toxic granules. In subsequent samples total leukocyte count of 66,100/mm³ and 47,400 mm³ was detected. As we had suspected sepsis we started the patient on broad spectrum antibiotics but his blood counts did not improve on subsequent evaluations. Blood culture showed growth of *Acinetobacter* species sensitive to cefoperazone. CSF culture and swab cultures from the ulcer sites did not show any growth. The C Reactive Protein (CRP) was positive and the first hour sedimentation rate was 6mm/hr.

In spite of a combination antibiotic therapy for 14 days patient had high leukocyte counts (47,400 mm³) and anemia (Hb=7.8mg/dl). Abdominal ultrasound and bone scans did not reveal any signs of local collection or arthritis. TORCH screening was negative. The strange clinical picture and leukemoid reaction prompted us to keep LAD I as a differential diagnosis for this neonate. The other differential diagnoses of neonatal leukemoid reaction, including antenatal administration of betamethasone, Down syndrome, preterm delivery, congenital leukemia and hyperviscosity syndrome were ruled out either by history and physical examination or by performing appropriate laboratory evaluations. The child had improved from omphalitis but the ulcers persisted. Blood was withdrawn for cytometry studies and the patient was discharged on request by the parents against medical advice. The parents were counseled regarding the severity and prognosis of suspected disease.

Flow cytometry using specific monoclonal antibodies revealed CD18 integrin (0.1% normal value = 100%) deficiency indicating severity of the disease.

A final diagnosis of LAD I was established by us on the basis of typical clinical features with regard to delayed separation of cord, leukocytosis and neutrophilia, antibiotic refractory periumbilical collection and decreased levels of CD 18 in flow cytometry. The patient also had classical features of gingivitis and periodontitis (Fig. 3) as described in patients with LAD I.

Discussion

Leukocyte adhesion deficiency disorders are a group of rare diseases characterized by molecular and clinical manifestations resulting from an impaired step in the inflammatory process, namely, the emigration of leukocytes from the blood vessels to sites of infection, which requires adhesion of leukocytes to the endothelium. This disorder is essentially inherited in an autosomal recessive pattern. Clinically presents as delayed separation of the umbilical cord, recurrent infections of mucous membrane of gastrointestinal tract and respiratory tract, and delayed wound healing in spite of neutrophilia. Three types of this disorder are described till date; LAD-I has the worst prognosis, patients hardly survive till their first birthday (7). This is caused by the lack of CD 18 integrins on the neutrophil cell surface.

In LAD II the main defect is in the rolling phase of the adhesion process. The precise mechanism leading to the severe psychological and growth retardation is still unknown. 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 retardation, short stature, and a distinctive facial appearance. Infections are generally not life-threatening and are usually treated in an out-patient clinic. There is no pus formation at the site of infection. It is usually seen that after 3 yr of age the infection frequency decreases & routine use of prophylactic antibiotics is not required (8). 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/mm³) is a constantly finding (9). LAD III only differs from LAD I by clinically presenting as severe bleeding tendency at delivery or later, otherwise both are somewhat similar (10).

Leukocyte adhesion deficiency usually presents with a leukocyte count 6 to 10 folds of normal values. Leukemoid reaction is defined as a WBC count exceeding 50000/mm³. Leukemoid reactions are usually neutrophilic and are most frequently associated with septicemia and severe bacterial infections including shigellosis, salmonellosis, and meningococemia. Infection in children with WBC adhesion defects results in WBC counts approaching or exceeding 100,000/mm³. Razvi *et al.* described "infants with delayed separation of umbilical cord attributable to urachal anomalies and suggested that this diagnosis should be considered in otherwise healthy infants before testing for leukocyte adhesion defects" (3, 11). In our case, both leukocytosis and leukemoid reaction were seen along with classical findings of LAD 1 including delayed cord separation, gingivitis and periodontitis (Fig. 3).

Leukocyte adhesion deficiency should be considered as differential diagnosis if a neonate present with delay in umbilical cord separation. The mean time of cord separation was reported between 5.8 and 10.9 days in many studies (12, 13). One should also consider the other causes of delayed separation of the cord, including prematurity, delivery by cesarean section, antibiotic administration in sepsis and others

(14). In this case, umbilical cord separated by 25th day of life.

Leukocyte adhesion deficiency should always be kept in mind when faced with a neonate with omphalitis and leukemoid reaction with delayed cord separation. In suspicious cases, prior to administration of vaccination a proper history and complete physical examination should be done.

Acknowledgement

The authors declare that there is no conflict of interest.

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