

## Case Report

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# Leukocyte adhesion deficiency type I in a term neonate with late onset sepsis: a case report

Laxman Basani\*, Roja Aepala

Department of Neonatology, Newborn Care Centre, Dolphin Children's Hospital, Hyderabad, Telangana, India

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**\*Correspondence:**

Dr. Laxman Basani,

E-mail: laxmanbasani@yahoo.co.in

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## ABSTRACT

Leukocyte adhesion deficiency (LAD) is a rare primary immunodeficiency disorder of leukocyte function characterized by marked leucocytosis secondary to lack of leukocyte recruitment at the site of infection. LAD type I results from lack of expression of leukocyte cell surface  $\beta 2$  integrins (CD 11 and CD 18) that are essential for leukocyte adhesion to endothelial cells and chemotaxis. LAD I is characterized by delayed separation of the umbilical cord, recurrent life-threatening infections of oral and genital mucosa, skin, intestine and respiratory tract. There is impaired pus formation and delayed wound healing despite extreme neutrophilia. Children with severe form of LAD I (<1% expression of CD18) have the worst prognosis and succumb to infections by 2 years of age. Study reports a case of LAD I in a term neonate who presented with sepsis and the diagnosis was confirmed by flow cytometry. Around 400 cases of LAD I were diagnosed worldwide so far, with very few cases reported from India.

**Keywords:** Delayed cord separation, Leukocyte adhesion deficiency, LAD I, Leucocytosis, Neonate, Sepsis

## INTRODUCTION

Leukocyte adhesion deficiency (LAD) disorders are autosomal recessive disorders characterized by marked leucocytosis. LAD I results from lack of cell surface expression of  $\beta 2$  integrins (CD 11 and CD 18) that are essential for leukocyte adhesion to endothelial cells.<sup>1,2</sup>

LAD I is characterized by delayed separation of the umbilical cord and recurrent life-threatening infections. Lack of leukocyte recruitment at the site of infection impairs pus formation and delays wound healing despite extreme neutrophilia.<sup>1,2</sup>

Children with severe form of LAD I (<1% expression of CD18) have the worst prognosis and succumb to infections by 2 years of age.<sup>3</sup> Children with mild form of LAD I (1-30% expression of CD18) may survive to adulthood.<sup>3</sup>

LAD II is caused by a genetic defect in fucosylation which presents early in life with infections and leucocytosis, but do not have delayed separation of the umbilical cord. These patients have severe mental retardation, short stature, a distinctive facial appearance and the rare Bombay (hh) blood phenotype.<sup>4</sup>

## CASE REPORT

A 3 week old full term neonate was referred to our hospital with infection that was not responding to antibiotics. Baby was born to a 24 year old primi gravida mother at 38 weeks gestation by caesarean section (Ind: preeclampsia). Apgar scores were normal and baby weighed 2780 grams at birth. Baby was breastfed. At 2 weeks of age, baby was admitted to a private hospital with fever (101.20F) and poor feeding. Septic screen was positive (CRP: 48 mg/l) and baby was given antibiotics.

Baby was referred for fever and thrombocytopenia not improving after 1 week of antibiotics.

At admission, baby was sick, febrile and irritable. There is periumbilical erythema with serous discharge from umbilicus and cord was still intact. He weighed 2960 grams, was febrile (101.80F), with HR of 154/min, CRT 3 sec, RR 56/min and SaO<sub>2</sub> of 94% in room air.

Laboratory investigations showed hemoglobin of 9.8 gm/dl, platelet count of 95,000/cu mm, leukocyte count of 70,300/cu.mm with a differential count of myelocytes 3%, band forms 10%, neutrophils 83%, lymphocytes 2% and monocytes 2%. Septic screen was positive (CRP: 78.2 mg/l). No abnormal cells were seen on the peripheral smear, but toxic granules were present. Serum LDH, leukocyte and neutrophil alkaline phosphatase were normal.

Blood culture grew E coli, sensitive to Meropenem and Levofloxacin. CSF was turbid and analysis showed 320 cells (neutrophils 90%; lymphocytes 10%), proteins of 382 mg/dl and glucose of 24 mg/dl suggestive of pyogenic meningitis. CSF culture was sterile. Leukocyte count remained elevated (91000/cu.mm) at the time of discharge.

Baby is a consanguineous product. Umbilical cord was still present at 3 weeks of age. With the characteristic clinical features of delayed umbilical cord separation, extreme neutrophilia and little pus in the presence of omphalitis, baby was investigated for leukocyte adhesion defects. Immuno phenotyping done on 4 color dual laser FACS Calibur by lyse wash technique showed complete absence of CD18, CD11a, CD11b and CD11 c antigens consistent with severe form of leukocyte adhesion deficiency (LAD I).

Baby was discharged after 3 weeks of antibiotics. Parents were counselled regarding bone marrow transplantation and risk of recurrent infections. One month after discharge, baby had another episode of infection and succumbed to sepsis.

## DISCUSSION

Leukocyte adhesion deficiency (LAD) is a rare autosomal recessive disorder with a prevalence of 1 in 1,000,000 births, characterized by recurrent infections.<sup>1,2</sup> First recognized in 1970s, around 400 cases of LAD have been identified worldwide so far. However, the actual number of cases would be higher because many patients succumb to infections before they are diagnosed due to lack of familiarity with LAD.

LAD I is characterized by recurrent bacterial infections, defects in neutrophil adhesion and delayed umbilical cord separation. Defects in adhesion result in poor neutrophil chemotaxis, diapedesis and phagocytosis. Infections such as omphalitis, pneumonia, gingivitis, periodontitis and

peritonitis are common and life-threatening. These infections are non-purulent as granulocytes cannot migrate to the sites of infection.<sup>3</sup> The white blood cell count is  $> 20 \times 10^9/l$  in the absence of infection which increases dramatically to  $40 - 160 \times 10^9/l$  with infections. Peripheral smear doesn't show any abnormal cells and diagnosis is established by studying the expression of CD11 and CD18 on leukocytes by flow cytometry.

LAD is classified into types I and II. LAD I is the most common, characterized by deficiency of  $\beta 2$  integrin subunit, also called CD18, of the leukocyte cell adhesion molecule which is mapped to chromosome 21q22.3.<sup>5</sup> CD18 is involved in making three other proteins (LFA-1,  $\alpha X \beta 2$ , and Mac-1/CR3), which allows neutrophils to make their way out of the blood stream by adhering to ICAM receptor on the apical surface of endothelial cells in the infected areas of the body.<sup>3</sup>

LAD II is caused by a genetic mutation in the specific transporter of fucose from the cytoplasm into the Golgi apparatus resulting in absence of SLeX and other fucosylated ligands.<sup>4,6</sup> Affected patients present early in life with infections and leukocytosis but do not have delayed separation of the umbilical cord. These patients also have severe mental retardation, short stature, a distinctive facial appearance and the rare Bombay (hh) blood phenotype.<sup>6</sup> LAD II cases have been reported only in people from Middle East and Brazil.

A variant of LAD, termed as LAD III is caused by a mutation in the KINDLIN3 gene which prevents  $\beta 1$ , 2 and 3 integrins from undergoing activation. Apart from infections and poor wound healing, they also have bleeding manifestations.<sup>7</sup>

Preimplantation genetic diagnosis (PGD) of LAD I offer promise. Mutational analysis on cells obtained by chorionic villous biopsy or amniocentesis can be done if familial mutation is known.<sup>8</sup> Leucocytes express  $\beta 2$  integrins CD18 and CD11 at 20 weeks of gestation. Fetal blood sampling and flow cytometry for CD18 on leucocytes establishes diagnosis when DNA analysis is not available. Gene therapy with insertion of CD18 sub unit is under investigation.<sup>9</sup> The only curative option available for severe form of LAD I patients is hematopoietic stem cell transplantation.<sup>10,11</sup> In LAD II patients, fucose supplementation reduces infections by improving phagocytic function, but does not improve the neurological outcome.<sup>12</sup>

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