2. Vanier MT, Millat G. Niemann Pick disease type C. Clin Genet 2003; 64: 269-281.

3. Kelly DA, Portmann B, Mowat AP, Sherlock S, Lake BD. Niemann-Pick disease type C: Diagnosis and outcome in children, with particular reference to liver disease. J Pediatr 1993; 123: 242-247.

4. Kruth HS, Vaughan M. Quantification of low-density lipoprotein binding and cholesterol accumulation by single human fibroblasts using fluorescence microscopy. J Lipid Res 1980; 21: 123-130.

5. Santhi P, Varma N, Marwah RK. Niemann Pick disease: Ultrastructural features. Indian Pediatr 2000; 37: 1017-1020.

6. Schneider AR, Stichling F, Hoffmann M, Scheler R, Arnold JC, Fiemann JF. Hepatosplenomegaly and progressive neurological symptoms–Late manifestation of Niemann-Pick disease type C–a case report. Z Gastroenterol 2001; 39: 971-974.

7. Millat G, Chikh K, Sleat DE, Fensom AH, Higaki K, Elleder M, *et al*. NPD type C: Spectrum of HE1 mutations and genotype/ phenotype correlations in the NPC-2 group. Am J Hum Genet 2001; 69: 1013-1021.

8. Karten B, Vance DE, Campenot RB, Vanle JE. Trafficking of cholesterol from cell bodies to distant neurone in Niemann Pick type C deficient neurons. J Biol Chem 2003; 278: 4168-4175.

9. Yamzaki T, Chang TY, Hass C, Shara Y. Accumulation and aggregation of amyloid beta protein in late endosomes of NPC cell. J Biol Chem 2001: 4454-4460.

10. Patterson MC, De Biseglie AM, Higgins JJ, Abel RB, Schiffmann R, Parker CC, *et al*. The effect of cholesterol lowering agents on hepatic and plasma cholesterol in NPC. Neurology 1993; 43: 61-64.

Leucocyte Adhesion Defect–1

K JOTHILAKSHMI
SUGANTHA PRIYA
JOHN MATTHAI

ABSTRACT

Leucocyte adhesion defect (LAD) is an inherited disorder of phagocytic function. It is characterized by inability of the leucocytes, in particular neutrophilis to migrate from the blood stream towards sites of inflammation. LAD -1 is characterized by the absence of b 2 integrins (CD 11 / CD18) on leucocytes. This disorder is characterized by delayed separation of the umbilical cord, recurrent severe infections, periodontitis, and delayed wound healing. We report an infant where the diagnosis was confirmed by flow cytometry.

Key words: *Immunodeficiency, Leucocyte adhesion defect.*

INTRODUCTION

Leucocyte adhesion defect (LAD) is an inherited immunodeficiency disorder characterized by the inability of the leucocytes to migrate from the blood stream towards the site of inflammation. Children with this rare disorder present with recurrent severe bacterial and fungal infections of the skin, oral, genital and respiratory mucosa accompanied by marked neutrophilia. Delayed separation of umbilical cord, diminished pus formation, poor wound

From the Department of Pediatrics, P.S.G. Institute of Medical Sciences & Research, Peelamedu, Coimbatore 641 004, Tamil Nadu, India.
Correspondence to: Dr. K. Jothilakshmi, Associate Professor, Department of Pediatrics, P.S.G Institute of Medical Sciences, Peelamedu, Coimbatore 641 004, India, E-mail: psg_peds@yahoo.com.

Manuscript received: June 28, 2007;
Initial review completed: October 30, 2007;
Revision accepted: December 24, 2007.

healing are characteristic. We report a case of LAD-I in a 5-month-old infant and to the best of our knowledge this is only the second report in an Indian child.

CASE REPORT

A 5-month-old male infant presented with history of recurrent fever from 15 days of age and progressive abdominal distension for one month. The present episode of fever had been for 8 days and had not responded to oral amoxicillin for 3 days followed by cefixime for 4 days. He was the second child of non-consanguinous parents born normally at term following an uncomplicated pregnancy. The elder sibling was a 3-year-old healthy girl. His birth weight was 3 kg. The umbilical cord had separated late on the 29th postnatal day even though there was no history suggestive of local infection. He was noted to be inactive with a poor cry and suck on the 5th day of life. His total WBC count was reported to be 55,460 / per mm^3 with neutrophilic leucocytosis. Blood culture grew *Pseudomonas* and he was given IV ceftazidime for 10 days. 3 weeks later he again had fever for 2 days which was treated by a local pediatrician with an oral antibiotic for 5 days. At 3 months of age, he developed fever and cough with breathing difficulty that needed hospitalization and ICU care at a local hospital. His WBC count was 72,840/mm^3 with strongly positive CRP. He also had oral thrush. Blood culture grew *S. aureus* and he was treated with cefotaxime for 7 days. He had attained social smile at 4 months and had not yet developed head control.

On examination the infant was febrile and inactive. His weight was 4.8 kg. He was pale. There was no icterus, edema or significant lymphadenopathy. There was oral thrush. The BCG site was still ulcerated. No dysmorphic features except for depressed nasal bridge. Liver was palpable 6 cm at right costal margin and spleen was palpable 3 cm along its long axis. Examination of other systems was normal.

The hemoglobin concentration was 7.4 g/dL. Total leukocyte count was 94,000 cell/cu mm with differential count of 77% polymorphs, 2% myelocytes, 7% band forms and 13% lymphocytes. Platelet count was normal. C Reactive protein was strongly positive. Blood culture grew *Streptococcus pneumoniae* sensitive to cefotaxime and amikacin. Liver and renal function tests were normal. Ultrasound abdomen revealed hepatosplenomegaly with normal echotexture. Bone marrow study was normal. Blood group was B negative and he was negative for Bombay phenotype. Serum immunoglobulin profile revealed IgG 1390 mg/dL (Normal for age: 200-900 mg/dL), IgM 477.5 mg/dL (Normal for age: 20-100 mg/dL) and IgA 173.1 mg/dL, (normal for age: 4-80 mg/dL). Serum complement and lactate dehydrogenase were normal. Flow cytometry was done on mononuclear cell population. Patient's values were as follows: For CD11a it was 0.29% (healthy control 95.4), for CD11b 2.47% (control 99.8), CD11c 0.48% (control 99.5) and for CD18 it was zero % (control 93.3). A diagnosis of LAD I was made based on the characteristic history, clinical features and positive flow cytometry. Baby was given antibiotics for 10 days. Parents were counseled about the nature of the illness and treatment options.

DISCUSSION

Leucocyte adhesion defect (LAD) is an inherited disorder of phagocytic function. The three different chains of the leucocyte integrin family (CD 11a,11b,11c) are dependent on one beta chain (CD - 18) for proper insertion into the cell membrane. Leucocyte adhesion defect type I (LAD I) results from the absence of beta 2 integrins (CD 11/CD 18) on leucocytes and most patients succumb to infections early in life. Patients with LAD II have normal CD 11/CD 18 integrins, but their neutrophils have defective N Glycosylation of surface proteins, which is essential for adhering to activated endothelial cells. While in LAD-I the integrin family is defective, in the LAD-II the selection system is involved(1). LAD affects nearly one out of every million individuals(2). A single case has been reported from Vellore, India(3). Inherited as autosomal recessive, LAD I and II are defects involving different steps in the adhesion cascade. LAD-I is characterized by severe bacterial and fungal infections, poor wound healing, marked granulocytosis and oral lesion (juvenile periodonitis). In addition, patients with LAD-II

suffer from severe growth and mental retardation and exhibit the rare bombay blood group. The association of delayed umbilical cord separation and LAD has been recorded in many cases(4,5). Delayed separation of the umbilical cord is however not pathognomonic, since it may occur when there is an underlying urachal abnormality(6). Laboratory studies include CBC which typically shows very high counts with every infection, sometimes even going up to 100,000/cumm. Immunophenotypic analysis of leucocytes (flow cytometry) is diagnostic. Children with LAD-I who have no detectable CD-18, as in our patient, have the worst prognosis(7).

Bone marrow and stem cell transplantation are current options in treatment. Long term prophylactic antibiotics and Gamma interferon have a supportive role(8). Gene therapy with insertion of the CD-18 subunit is currently under investigation. Prenatal diagnosis is possible by identifying the absence or deficiency of leucocyte cell adhesion molecule (leu CAM's) on the leucocyte membrane, using monoclonal antibodies(9).

ACKNOWLEDGMENT

We thank Dr Alok Srivastava, Professor of Hematology, CMC, Vellore for performing the flow cytometry.

Contributors: KJ, JM, SP worked up the patient clinically. KJ and JM reviewed literature and drafted the manuscript. JM and KJ co-drafted and revised the manuscript. KJ will act as the guarantor.

Funding: None.

Competing interests: None stated.

REFERENCES

1. Etzioni A, Tonetti M. Leucocyte adhesion deficiency II from A to Z. Immunol Rev 2000; 178: 138-147.
2. Akbari H, Zadeh MM. Leucocyte adhesion deficiency. Indian J Pediatr 2001; 68: 77-79.
3. Simon A, Pillai S, Raghupathy P, Chandy M. Leucocyte adhesion deficiency 1. Indian Pediatr 2002; 39: 963-966.
4. Hayward AR, Leonard J, Wood CBS, Harvey BAM, Greenwood MC, Soothil JF. Delayed separation of the umbilical cord, widespread infections and defective neutrophil mobility. Lancet 1979; 1: 1099-1101.
5. Etzioni A, Harlan JM. Cell adhesion and leukocyte adhesion defects. In : Ochs HD, Smith CIE, Puck JM, eds. Primary Immunodeficiency Diseases: A Molecular and Genetic Approach. New York, NY: Oxford University Press; 1999. p. 375-387.
6. Razvi S, Murphy R, Rundles. C, *et al.* Delayed separation of the umbilical cord attributable to urachal anomalies. Pediatrics 2001; 108: 493-494.
7. Anderson DC, Schalsteig FC, Finegold MJ, Hughes BJ, Rothlein R, Miller LK, *et al*. The severe and moderate phenotypes of heritable Mac-1, LFA-1 deficiency: their quantitative definition and relation to leukocyte dysfunction and clinical features. J Infect Dis 1985; 152: 688-689.
8. Weening RS, Bredius RG, Vomberg PP, van der Schoot CE, Hoogerwerf M, Roos D, *et al*. Recombinant human interferon gamma treatment in severe leucocyte adhesion deficiency. Eur J Pediatr 1992; 151: 103-107.
9. Bauer TR Jr, Hickstun DD. Gene therapy for leukocyte adhesion deficiency. Curr Opin Mol Ther 2000; 2: 383-388.