

Case Report

Leucocyte Adhesion Deficiency Type 1 in a Bedouin Child: First Reported Case from Kuwait

Nada AM Al-Terkait, Dina G Ramadan, K C Aboobacker
Department of Pediatrics, Al-Sabah Hospital, Kuwait

The Kuwait Medical Journal 2001, 33 (1): 65-67

INTRODUCTION

Leucocyte adhesion deficiency (LAD) is a rare autosomal recessive immunodeficiency disorder characterized by recurrent and/or chronic bacterial and, occasionally, fungal infections without pus formation despite persistent leucocytosis^[1]. In affected subjects, leucocytes have abnormal migration and adherence, as a result of CD11/CD18 leucocyte glycoprotein deficiency, rendering patients susceptible to life-threatening infections. In its most severe form, it is usually fatal^[2]. Leucocyte adhesion deficiency type 1 (LAD-1) was first described as a separate entity among immunodeficiencies in 1979 by Hayward et al^[3,4].

In this report, we describe our experience with a Bedouin boy with severe and recurrent infections due to LAD-1. A Medline search of indexed journals failed to find any case of LAD-1 reported from Arab countries. To the best of our knowledge, this is the first reported case from Kuwait.

CASE REPORT

The propositus is a male child born in July 1998, after an uneventful pregnancy and delivery. He is the second child of healthy, first-cousin Bedouin parents. At the age of 10 days, his umbilical cord detached spontaneously. From birth onward, a persistent leucocytosis (mainly granulocytosis) and bouts of non-purulent inflammatory lesions characterize his history. His first admission in our unit, at the age of 32 days, was for staphylococcal scalded skin syndrome (SSSS), which required an extended high dose course of intravenous antibiotic therapy. Since then, he has continued to have low-grade skin infections with minor abscesses, impetigo, and Candida skin infections requiring topical antibiotics and antifungal treatment, and systemic antibiotics (cotrimoxazole and erythromycin). Wound healing has taken place very slowly. In addition, he has had frequent admissions in our unit due to bacterial infections such as pneumonia, chronic discharging otitis media with

nasal septum perforation, infected toe ulcer following trauma to foot with delayed healing, perianal skin abscess and several bouts of sepsis due to various organisms (*S. aureus*, *E. coli*, *Klebsiella*, Yeast cells, *Enterococcus faecalis*, -haemolytic *Streptococci* and *Pseudomonas aeruginosa*). He required intravenous treatment with high doses of combined antibiotic therapy for these infections. *Pseudomonas* was the most frequently isolated organism from the right ear, several attempts to eradicate it with intravenous therapy and surgical drainage under general anesthesia failed. Eventually the infection was successfully suppressed by prolonged therapy with oral Ciprofloxacin. The child's development is normal except for a speech delay. He was fed on breast milk and mixed diet and his vaccination schedule was incomplete due to frequent hospital admissions.

During the last follow up in our clinic in July 2000, the patient was found to be below the 5th percentile for height, his weight improved from the 5th to the 10th percentile, and his head circumference improved from the 10th to the 25th percentile. Skin showed pallor, healed scars of impetigo over the groin and lower abdomen (Fig. 1), and a big hypopigmented scar on the right upper back related to the previous SSSS (Fig. 2). The right ear was wet with serous non-purulent discharge. The nose showed a healed nasal septum. The throat showed mild oral thrush with both tonsils present. No clubbing. No dysmorphic features. No lymphadenopathy. No palpable liver or spleen. Systemic examination was otherwise unremarkable.

Investigation of this patient revealed a persistent leucocytosis in the range of 20-70 x 10⁹/L, mostly granulocytosis. Hemoglobin was fluctuating between 7 and 11g/dl due to iron deficiency anemia and severe infections. He required a twice-irradiated RBC transfusion but when he developed a febrile reaction and irritability with it, the transfusion was stopped

Address correspondence to:

Nada Al-Terkait, Dept. of Pediatrics, Al-Sabah Hospital, PO Box: 40788, Kuwait. Tel: (965) 533 5353; fax: (965) 483 5805

Table 1
Immunoglobulin electrophoresis results

Age (months)	IgG g/L	IgA g/L	IgM g/L	IgG1 g/L	IgG2 g/L	IgG3 g/L	IgG4 g/L
2	2.76 *(3.0-8.0)	<0.07 (0.01-0.4)	0.50 (0.19-0.76)	1.47 (1.8-6.7)	0.871 (0.38-2.1)	0.433 (0.14-0.7)	0.797 (<0.03-0.36)
3	3.44 (2.5-6.6)	0.12 (0.1-0.59)	0.84 (0.19-0.86)				
4				12.0 (1.8-6.7)	5.8 (0.38-2.1)	0.9 (0.14-0.7)	0.78 (<0.03-0.36)
5				15.3 (1.8-7.0)	1.5 (0.34-2.1)	1.0 (0.15-0.8)	0.17 (<0.03-0.23)

* Refers to reference ranges for age

prematurely. Immunological evaluation revealed the following results: Serum immunoglobulin levels-as shown in Table 1. Nitroblue tetrazolium (NBT), IgE, Leucocyte alkaline phosphatase, C3, C4 and CH100: Normal. Immunophenotyping revealed normal expression of CD3, CD4, CD8, CD16/56, and CD19, no expression of both CD11b and CD18, which is diagnostic of leucocyte adhesion deficiency type 1.

DISCUSSION

LAD refers to two types of blood cell adhesion disorders (LAD-1 and LAD-11) leading to life threatening recurrent infections^[4-8]. LAD-1 affects about 1 in 1,000,000 individuals and is characterized by recurrent bacterial and fungal infections with muted inflammatory response, a reduced neutrophil accumulation at sites of infection and an extreme increase in circulating neutrophil count. LAD-1 results from mutations in the gene on chromosome 21q22.3 encoding CD18, the 95-kDa α leucocyte integrin subunit^[7].

In this report, we describe the findings of a patient with clinical features of moderate to severe LAD-1 disorder^[6]. A delay in the natural detachment of the umbilical cord is often the first sign of this disorder and may result in serious omphalitis caused by manipulations^[4]. Our patient had dry separation of the umbilical cord without undue problems. His presentation with severe life-threatening infections such as staphylococcal scalded skin syndrome (SSSS) in association with severe persistent granulocytosis is classical of this disease. The recurrent skin abscesses, perianal abscess, pneumonia, and chronic discharging otitis media (caused by *Pseudomonas aeruginosa*) occurring in our patient along with non-purulent bacterial infectious foci, and impaired wound healing are also typical clinical features. Skin infections, that may progress to large chronic ulcers that become polymicrobial in character including anaerobic organisms, are slow to heal requiring



Fig. 1: Healed scars of impetigo over the groin and lower abdomen



Fig. 2: Old scars of previous SSS syndrome

months of antibiotic treatment and often plastic surgical grafting^[7].

LAD-1 is characterized by absence of the α integrins (CD11/CD18) on leucocytes^[4]. This group of leucocyte integrins is responsible for the tight adhesion of neutrophils to the endothelial cell surface, and for the adhesion to opsonized microorganisms to promote phagocytosis and activation of the NADPH oxidase^[7].

When expression is completely absent or greatly reduced, patients often die within the first year of life^[2,9]. A low level of α expression, however, may result in a milder clinical picture of recurrent infection, which offers a better prognosis^[10].

Treatment of LAD-1 depends on the phenotype as determined by the level of expression of functional CD11/CD18 integrins. Early allogeneic Bone Marrow Transplantation is the recommended treatment for severe LAD-1 associated with complete absence of the CD11/CD18 integrins^[7,11]. Our patient has severe

LAD-1 and the option for Bone Marrow Transplant was considered but was rejected by the family for financial reasons. Patients with both severe and mild forms of LAD-1 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, as is very prolonged antibiotic treatment for indolent infections. Previous trials of using recombinant human interferon-gamma treatment were not encouraging, as they did not control severe leucocyte adhesion deficiency^[12]. When successful Gene Replacement Therapy is available^[13], LAD-1 will be an ideal disease for this form of therapy because the clinical history of the mild form of LAD-1 suggests that even a low level correction of neutrophil adhesion disorder would likely provide clinical benefit^[7].

CONCLUSION

Recurrent infections with persistent polymorph leucocytosis in an infant should alert the pediatrician to consider immune deficiency disorders including leucocyte adhesion deficiency and thus to initiate the necessary immunological evaluation for prompt diagnosis and management.

ACKNOWLEDGMENTS

Our sincere appreciation to our ward nurses and doctors for their great support and care of this child in the ward and also to professor Gareth Morgan, Consultant Pediatric Immunologist at the Pediatric Department, Kuwait University, for his valuable advice.

REFERENCES

1. Schleimer RP, Bochner BS. The role of adhesion molecules in allergic inflammation and their suitability as targets of antiallergic therapy. *Clin and Exp Allergy* 1998; 283 (Suppl 3):15-23.
2. Schwartz BR, Wayner EA, Carlos TM, Ochs HD, Harlan JM. Identification of surface proteins mediating adherence of CD11/CD18 deficient lymphoblastoid cells to cultured human endothelium. *J Clin Invest* 1990; 85:2019-2022.
3. Hayward AR, Leonard J, Wood CBS, Harvey BAM, Greenwood MC, Soothill JF. Delayed separation of the umbilical cord, widespread infections, and defective neutrophil mobility. *Lancet* 1979; 1:1099-1101.
4. Kuijpers TW, Van Lier RAW, et al. Leukocyte adhesion deficiency type 1(LAD-1)/Variant: dysfunctional B2: Integrins. *J Clin Invest* 1997; 100:1725-1733.
5. Kerkhof PC, Weemaes CM. Skin manifestations in congenital deficiency of leucocyte-adherence glycoproteins (CDLG). *BR J Dermatol* 1990; 123:395-401.
6. Parent C, Eichacker PQ. Neutrophil and endothelial cell interactions in sepsis. The role of adhesion molecules. *Infect Dis Clin North Am* 1999; 13:427-447.
7. Malech HL, Nauseef WM. Primary inherited defects in neutrophil function: etiology and treatment. *Seminars in Hematology* 1997; 34:279-290.
8. Becker DJ, Lowe JB. Leukocyte adhesion deficiency type 11. *Biochim Biophys Acta* 1999; 1455(2-3):193-204.
9. Gahmberg CG. Leukocyte adhesion: CD11/CD18 integrins and intercellular adhesion molecules. *Current Opinion in Cell Biology* 1997; 9:643-650.
10. Davies KA, Toothill VJ, Savill J et al. A 19-year-old man with leucocyte adhesion deficiency. In vitro and in vivo studies of leucocyte function. *Clin Exp Immunol* 1991; 84:223-231.
11. Fischer A, Haddad E, Jabado N et al. Stem cell transplantation for immuno-deficiency. *Springer Seminars in Immunopathology* 1998; 19:479-492.
12. Weening RS, Bredius RG, Vomberg PP et al. Recombinant human interferon-gamma treatment in severe leucocyte adhesion deficiency. *Euro J Pediatr* 1992; 151:103-107.
13. Malech HL, Bauer TR Jr, Hickstein DD. Prospects for gene therapy of neutrophil defects. *Seminars in Hematology* 1997; 34:355-336.