Leukocyte adhesion defect: A rare cause of immunodeficiency

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Abstract

Leukocyte adhesion deficiency 1 (LAD-1) is a rare autosomal recessive disorder of leukocyte function due to integrin deficiency. It is characterized by recurrent bacterial and fungal infections and depressed inflammatory responses despite striking blood neutrophilia. Severe LAD usually presents early in infancy. Here, we report a case who presented late with symptoms of LAD-1 when compared with earlier reported cases and without the usually associated infections.

Key words: Autosomal recessive, Integrin, Leukocyte adhesion defect, Neutrophilia

Leukocyte adhesion defect is a rare form of immunodeficiency disorder with an incidence of 1 in 10 million individuals [1]. It is usually characterized by recurrent bacterial and fungal infection. Patients with leukocyte adhesion deficiency (LAD) have impaired neutrophil chemotaxis leading to neutrophilia and absence of pus formation [1]. Children with severe LAD-1 disease are normally infants with recurrent, indolent bacterial infections of the skin, mouth, respiratory tract, lower intestinal tract, and genital mucosa. We are reporting a case of this disorder with late presentation and without the usually associated infections. To the best of our knowledge, this is the third case of LAD-1 reported in Indian children who have late presentation.

CASE REPORT

A 20-month-old developmentally normal female toddler born out of non-consanguineous marriage brought with high-grade fever (104°F) of 2 days. Her systemic examinations were normal including eyes, ears, nose, mouth and throat with no dysmorphic features [1]. Her weight was 12.4 kg; length was 83.7 cm and HC 48 cm (normal for her age). She was born to a primi mother at hospital with birth weight of 2.78 kg with uneventful antenatal and postnatal period and history of cord separation at day 5 with no significant family history. Her immunization was up to date, and she was otherwise growing well.

This was the third hospital admission within a span of 6 months (first admission at 14 months of age), each time for fever without focus. Her anthropometric parameter remained within normal range with no weight loss over a period of 6 months. On laboratory investigations, complete blood count showed leukocytosis and striking neutrophilia (total leucocyte count [TLC] - 32,700/mm³ and neutrophil 23,544/mm³) at the time of first admission. Subsequently, her TLC decreased after a course of antibiotic (ceftrioxone for 7 days), but remained in high range (26,000/mm³) with neutrophil count of 18,000/mm³ during afebrile period. At second admission (age 17 months), her TLC was 56,000/mm³ with predominant neutrophils (absolute neutrophil count = 45,846/mm³). She was treated with broad spectrum antibiotics injection cefrioxone and amikacin for 7 days. Echocardiogram was not done and parents did not give consent for bone marrow examination.

On this admission (age 20 months), the peripheral neutrophil count was 24,092/mm³. Other investigations done to search the focus including blood culture, urine routine, urine culture, chest X-ray and ultrasonography (kidneys, ureters, and urinary bladder) were normal on all three occasions. Erythrocyte sedimentation rate was 20-25 mm/h, C-reactive protein was elevated (36-128 mg/dl) in all three admissions. She was treated with piperacillin and tazobactam plus amikacin for 10 days and investigated for immunodeficiency.

Her CD4/CD8 was 3.14 (normal: 1.2-6.2), human immunodeficiency virus enzyme-linked immunosorbent assay negative, serum immunoglobulin G was 823 mg/dl (normal for age: 290-1070 mg/dl), IgM 72 mg/dl (normal: 40-150 mg/dl), IgA 58 mg/dl (normal: 15-90 mg/dl) and serum IgE level was 126.36 mg/dl (normal <35.00), which was not significantly raised. Nitroblue-tetrazolium was also negative, and there were no Chediak–Higashi granules on peripheral smear. CD11a/CD18 was 13.3% (control 48.2%), CD11b 97.4% (control 93.4%), and CD11c/CD18 96.7% (control 94.5%) by flow cytometry method leading to diagnosis of LAD-1. Since, March 2013 she is on cotrimoxazole prophylaxis and currently asymptomatic and growing well with weight for age 15.4 kg.
and length for age 97.3 cm at 36 months of age with neutrophil counts (4420/mm³). Parents were counseled regarding the nature of disease and treatment options available.

DISCUSSION

Leukocyte adhesion defect is an autosomal recessive immunodeficiency disorder [1]. It was first recognized as a clinical entity in 1970. Neonates with LAD-1 may have a history of delayed cord separation [2-4], usually with associated infection (omphalitis) [1]. The adhesion defect leads to poor neutrophil chemotaxis, phagocytosis and neutrophilia [3]. Individuals with LAD suffer from bacterial infections beginning in the neonatal period. Infections such as omphalitis, pneumonia, gingivitis and periodontitis are common and often life-threatening due to the infant’s inability to properly destroy the invading pathogens [2-3]. These individuals do not form an abscess because granulocytes cannot migrate to the sites of infection.

The inherited molecular defect in patients with LAD is a deficiency of the β-2 integrin sub-unit, also called CD18, of the leukocyte cell adhesion molecule, which is found on chromosome 21 [1]. This defective gene creates a non-functioning protein resulting in lack of lymphocyte function-associated antigen 1 integrin (CD11a/CD18), which allows neutrophils to make their way out of the blood stream by adhering to the Ig family receptor intercellular adhesion molecule 1 on the apical surface of endothelial cells in the infected areas of the body [5]. The bacteria can then proliferate, leading to symptomatic infection. The infection can then spread unimpeded and cause serious injury to important tissue. In LAD-1, the integrin system is defective while in LAD-2, selectin system is defective [1]. The four different chains of the leukocyte integrin family (CD11a, 11b, 11c, CD11d) are dependent on one beta chain (CD-18) for proper insertion into the cell membrane [1]. Mutations in the CD18 gene either impair gene expression or affect the structure of synthesized CD18 peptide, leading to functionally abnormal CD11/CD18.

In general, diagnosis is done after several preliminary tests of immune functions, including basic evaluation of the humoral immune system and the cell-mediated immune system. A WBC differential will reveal extremely elevated levels of neutrophils (on the order of 6-10 × normal) because they are unable to leave the blood vessels. Patients with severe form of LAD-1 have <0.3% of the normal amount of β2-integrin molecules, whereas patients with moderate phenotype may have 2-7% of the normal amount [1]. The severity of infectious complications correlates with a degree of β-2 integrin deficiency. Patients with moderate deficiency have an infrequent life-threatening infections and relatively long survival [1,5]. In our case it was 13.3%, which probably explains the late presentation and fever without focus and behaved like milder form of moderate LAD-1.

Once the diagnosis of a severe LAD is made, bone marrow transplantation is the current standard cure [6]. However, some progress has been made in gene therapy, an active area of research [7]. Antibiotic prophylaxis and gamma interferon have a supportive role [7]. Patients can be maintained on trimethoprim-sulfamethoxazole prophylaxis and should have close surveillance for early identifications of infections and initiations of empirical treatment with broad spectrum antibiotics [1]. Prenatal diagnosis is possible by identifying deficiency or absence of leukocyte adhesion (leu CAM) on leukocyte using monoclonal antibody [8].

The normal neonatal period with late presentation as fever without focus with peripheral neutrophilia makes our case unique. To the best of our knowledge, this is the third case reported in an Indian child [9]. Having a high index of suspicion even in the absence of typical clinical features of this disorder may lead to early evaluation and diagnosis.

REFERENCES


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