Leukocyte Adhesion Deficiency: First Case Report from Bangladesh

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ABSTRACT

Leukocyte Adhesion Deficiency (LAD) is an autosomal recessive immunodeficiency disorder characterized by failure of leukocyte to adhere to endothelium resulting in recurrent overwhelming infection from childhood. Deficiency of CD18 expression due to mutation of beta-2 integrin results in LAD. Persistent neutrophilia without infection and leukemoid reaction during infection is hallmark for LAD. Based on percentage of CD18 expression it can be divided into three types (mild, moderate and severe). Diagnosis requires flow cytometric measurement of CD 18, CD11a, CD11b and CD15a or mutation analysis. We are presenting a 4-year-old female baby with recurrent skin and soft tissue infection. Diagnosis was suspected by history, physical examination and blood reports and confirmed by flow cytometric measurement of CD18 expression. It reveals LAD type-I severe variety. Allogenic stem cell transplant is the only recommended option for LAD. In other cases, antibiotic and antifungals are the mainstay of conservative management.

Keywords: Leukocyte Adhesion Deficiency, LAD-I, CD18 deficiency, Beta-2 integrin mutation

Background

Leukocyte Adhesion Deficiency (LAD) is a rare autosomal recessive primary immunodeficiency disorder. It is characterized by inability of leukocyte to migrate from blood stream to infection site due to deficiency of protein needed for adhesion to endothelium. LAD was first described in the medical literature in 1979. There are around 300 reported cases all over the world and described incidence is about 1 per million. It occurs due to deficiency of CD18 caused by mutation of beta-2 integrin and divides into three phenotypes depending upon extent of expression of CD18 on leukocyte surface. Expression of 2-20% antigens is found in mild to moderate types and, less than 2% in severe type. Despite frequent infections, mild and moderate types may survive to adulthood. However, severe LAD-I is associated with significant mortality (reported as 75% by the age of 2 years), if no specific intervention has been done. The goal of therapy is to minimize infections. LAD-I patients
also develop keloids and have problems forming scar tissue because of defective monocyte function. Prenatal diagnosis of LAD-I can be established in families in which the mutation of the two CD18 alleles are known.\textsuperscript{3,4} In some cases, white blood cell (granulocyte) transfusions may be required to treat life-threatening infectious complications. Because of adverse events, white blood cell transfusions are seldom used when all other therapeutic options have failed. In a recent publication the overall survival of individuals who have had a bone marrow transplant for LAD-I is almost 75\%.\textsuperscript{5} We are reporting here the first case from Bangladesh.

**Case presentation**

A 4-year-old female (DOB: 28/04/2017) from a rural area of Bangladesh presented with skin and soft tissue infection. She was child of consanguineous marriage between first degree cousins. She was born at term by cesarean section, showed no obvious dysmorphism and suffered from no neonatal complication. She had a history of umbilical cord infection on day 3 of birth and was treated with intravenous antibiotics and umbilical cord was detached on 11th day. At the 18th month of her age, she was admitted with extensive non healing ulcer over back of left thigh. Routine tests and culture of the wound swab revealed neutrophilic leucocytosis and growth of pseudomonas in the wound. She was treated with antibiotic as per sensitivity but ulcer partially improved. She had undergone skin grafting two months later, healing was good except hypertrophy and keloid formation (Figure 1a). She again developed another skin ulcer (2x1.5 cm) in posterior side of right thigh with oozing and crusting, regular margin, surrounding hyperpigmentation and scarring at the age of three and a half year (Figure 1b).

**Figure 1:**
- a) Keloid formation after skin graft;
- b) Pus free skin ulcer under right thigh;
- c) Right forearm skin ulcer Figure
Antibiotic was started but response was not optimum. She was suspected as LAD on clinical basis and was advised for further investigations to confirm the diagnosis. This was delayed due to COVID pandemic situation as all outsource testing facility remained close. Two months later another skin ulcer (1x1 cm) developed in right forearm (Figure 1c). LAD-I deficiency was found by flow cytometry and diagnosis of LAD type I was confirmed.

**Investigations**

Blood reports revealed liver, kidney thyroid functions were normal. Immunoglobulin assay showed no deficiency. Pattern of leucocytosis is shown in Figure 2.

![Figure 2: Pattern of Leukocytosis](image)

Flow cytometry was performed on a mononuclear cell population, showing deficiency of CD 18, CD 11a, CD 11b and CD 15a (Table I). The antibodies used for each integrin in the flow cytometry analysis are from Becton Dickinson.

**Table I: Leucocyte Adhesion Deficiency (By Flow Cytometry)**

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Results</th>
<th>Units</th>
<th>Bio. Ref. Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD 18</td>
<td>0.60</td>
<td>%</td>
<td>98.00-100.00</td>
</tr>
<tr>
<td>CD 11a</td>
<td>0.10</td>
<td>%</td>
<td>93.00-100.00</td>
</tr>
<tr>
<td>CD 11b</td>
<td>0.60</td>
<td>%</td>
<td>93.00-100.00</td>
</tr>
<tr>
<td>CD 15a</td>
<td>94.50</td>
<td>%</td>
<td>91.00-100.00</td>
</tr>
</tbody>
</table>

**Discussion**

Immune system is essential for protection of body from invading organism like bacteria, virus, and fungus. Leucocytes are primary component of immune system. To fight against infection neutrophil needs to migrate to inflammatory site after adhering to endothelium. Adhesion is the crucial step which is missing in LAD as there is deficiency of adhesion molecule. As they fail to reach at the site of need, local pus formation is not possible and subsequently wound healing hampers. So recurrent infection is evident from early
childhood. LAD may be manifested by omphalitis, delayed separation of umbilical cord, periodontitis, skin and soft tissue infection, pyoderma gangrenosum like wound, non-purulent infection foci, dry gangrene, impaired wound healing. Common organism includes Staphylococcus, Pseudomonas, Klebsiella, Enterococcus, Proteus and Escherichia coli. Persistent neutrophilia in the absence of infections and significantly increased myeloid leucocyte counts in the presence of infections are characteristic. Although a higher median WBC count were reported by Novoa et al. in 143 cases with CD18 <2% (48 versus 30×10⁹/L) a limited correlation was found between CD18 expression and WBC counts for the entire cohort.

Novel mutations in ITGB-2 gene required for encoding of CD18 subunit of the beta-2 integrins results in failure of leucocytes to link to endothelium and transportation to inflamed or infected site. This condition is an autosomal recessive disorder carrying both copies of the gene mutated. As parents carry one copy of the mutated gene, they are typically symptom free and remain undiagnosed. The ITGB-2 is located at the long arm of chromosome 21q22.3, and more than 80 mutations are identified till date. The severity of the clinical manifestations is directly related to the degree of CD18 deficiency. Deficient expression of any of the subsequent four members of the β2 integrin subfamilies leads to LAD-I syndrome: αLβ2 (CD11a/CD18 and LFA-1), αMβ2 (CD11b/CD18, MAC-1, and CR3), αXβ2 (CD11c/CD18, and p150/95), and αDβ2 (CD11d/CD18).

For LAD-I patients with severe disease allogeneic stem cell transplant with the best available match is the only hope till date. LAD-I patients with moderate disease (CD18 expression 2.5 to 10%), often respond to conservative therapy with prompt antibiotic use for active infections and prophylactic antibiotics. However, they will have still a significant risk of death from overwhelming infection, and stem cell transplantation should be considered depending upon individual situation.

Conclusion

To the best of our knowledge, this is the first reported case of LAD type 1 in Bangladesh. We considered the possibility of bone marrow transplantation, which is restricted by the limited financial ability of family.

References