Leukocyte adhesion deficiency type 1 with normal expression of CD 11a, CD11b and CD11c

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ABSTRACT

Leukocyte Adhesion Deficiency Type I (LAD-I) is a rare autosomal recessive disorder resulting from ITGB2 gene mutations on long arm of chromosome 21. This mutation disrupts leukocyte migration, causing impaired wound healing, recurrent infections, periodontitis, delayed umbilical cord separation and neutrophilic leukocytosis. Diagnosis involves flow cytometry to assess CD18, CD11a, CD11b, and CD11c surface expression, along with gene mutation analysis. Early detection and management are crucial for those with LAD-I. Here, we present a case of 11 years old male child with recurrent skin infections and diagnosed with rare phenotype of LAD-1 with normal expression of CD11a, CD11b and CD11c. This case improved our understanding of the mild and delayed presentation of Leukocyte Adhesion Deficiency Type 1 (LAD-I) with variable CD marker expression. It highlights the value of using flow cytometry methods to diagnose inborn errors of immunity, highlighting the need for continued study and increased awareness in this area. Increased knowledge of the various phenotypic expressions of LAD-I among medical professionals and researchers could facilitate prompt diagnosis and treatment, ultimately leading to better outcome and improved quality of life in patients.

Keywords: Adhesion molecules, Flow-cytometric analysis, Integrins, Leukocyte adhesion deficiency, Molecular analysis

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INTRODUCTION

Leukocyte adhesion deficiency Type I (LAD-I) is a rare inborn error of immunodeficiency resulting from mutations in ITGB2 genes located on long arm of chromosome 21, specifically coding for CD18. It follows an autosomal recessive inheritance pattern [1].

Patients with LAD-1 have very high mortality, about 75% of the patient die before the age of 2 years and both genders are affected equally [2]. LAD-I results from the absence of CD18 expression, a shared subunit in beta 2 integrins: CD11a/CD18 (LFA-1), CD11b/CD18 (Mac 1 or CR3), and CD11c/CD18 (CR4).

Individuals with LAD-I face heightened vulnerability to recurrent bacterial infections, non-purulent abscesses, impaired wound healing, neutrophilic leukocytosis and potentially death if left untreated. Neutrophils release from the bone marrow is normal but their migration from blood to infection sites is compromised. Three distinct leukocyte adhesion deficiency types have been recognized. Diagnosis primarily relies on flow cytometric analysis of neutrophils for surface expression of CD18 and CD11. Prophylactic antibiotics and interferon gamma have shown less response to the disease. Bone marrow transplantation is the treatment of choice in leukocyte adhesion defect (LAD) with a very high success rate. Gene therapy with insertion of the CD18 subunit is currently under trial [3].

CASE REPORT

A 11 years old male child, the second offspring of consanguineous parents living in

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Rawalpindi, Punjab, sought evaluation for immunodeficiency at the Department of Immunology, Armed Forces Institute of Pathology due to recurrent skin and chest infections. The infant, weighing 2.8 kg at full term and delivered by cesarean section, his umbilical cord was separated on 9th day of postnatal life. He received immunizations under the expanded program of immunization (EPI) in Pakistan. Recurrent infection started at the age of six months, with a serious gastrointestinal infection and progressed to milder skin and chest infections. Around 7 years of age, the frequency of skin infections increased. The older sibling of the child likewise suffered from severe chest and skin illnesses, eventually passed away at the age of 11 years from sepsis.

On general physical examination, the child revealed that there were no oral or cutaneous ulcerations, pallor or cyanosis. The spleen and liver were not enlarged. A blood complete picture showed that the platelet count was 504 x 10^9/L, the hemoglobin level was 9.9 g/L, and the total leukocyte count was 17,100/µL (comprising 60% neutrophils). Neutrophils analysis on flow cytometric analysis showed the complete absence of CD18 but normal expression of the surface markers CD11a, CD11b, and CD11c (Figure-I). Because of the unique nature of this phenotype at our center, additional verification was obtained via DNA testing by sending samples at a private laboratory in Germany. A homozygous pathogenic variation, c.1777C>T (p.Arg593Cys), in the ITGB2 gene was identified by whole exome sequencing, supporting the diagnosis of leukocyte adhesion deficiency type I (LAD-I).

This LAD-I patient presented with milder infections, normal umbilical cord separation and blood complete picture also not showing the typical features of neutrophilia leukocytosis and hence missed early diagnosis. Presently, the patient is receiving prophylactic antibiotics, and the process of HLA matching for bone marrow transplantation is underway.

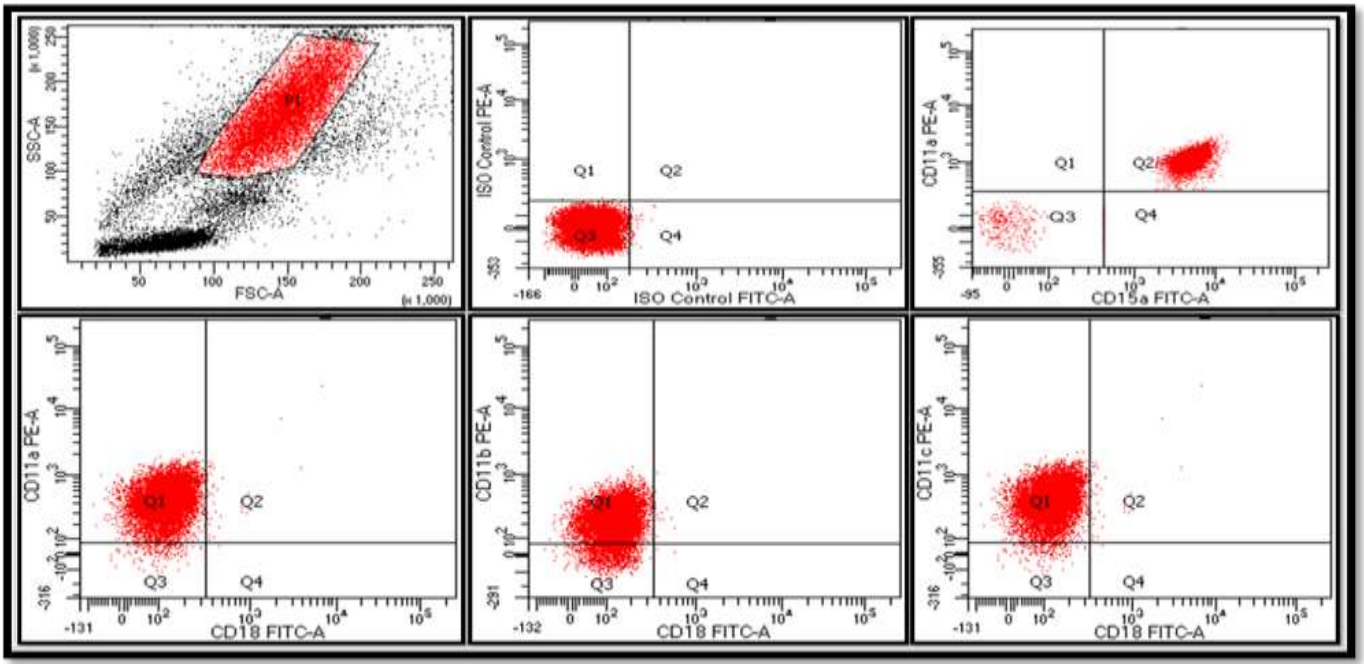

Figure-I: Flow cytometric analysis for Leucocyte Adhesion Deficiency Type I.

DISCUSSION

Leukocyte adhesion deficiencies constitute a group of autosomal recessive disorders characterized by defective leukocyte and endothelial adhesion molecules, leading to inability of leukocytes especially neutrophils to efficiently migrate to site of infection. This deficiency results in recurrent infections in early life. The three types of adhesion molecule deficiencies are categorized as LAD-I, LAD-II, and LAD-III [4].

In LAD-I, patients fail to express the beta chain of beta-2 integrins, encoded by the CD18 gene on chromosome 21's long arm. Notable

beta-2 integrins include leukocyte function associated antigen 1 (LFA-1 or CD11a/CD18), Mac-1 (CD11b/CD18), and P150, 95 (CD11c/CD18) [5]. A case report already published in 2019 in Pakistan which showed absence of CD18, CD11c with low expression of CD11b [6]. A multi-center study conducted in India and published in 2019 showed that CD18 expression varied from absent to normal but CD11a expression was absent in all tested 127 patients [7]. Another multi-center study published by Wolach B *et al* in 2016 also showed CD11a was near absent in all cohort of the study [8] whereas this rare case of leukocyte adhesion defect showed normal expression of CD11a, CD11b and CD11c.

This case highlighted the variety of clinical manifestations and diagnostic challenges associated with Leukocyte Adhesion Deficiency Type I (LAD-I). Unlike traditional cases, which are distinguished by severe skin and chest infections, delayed umbilical cord separation and distinctive laboratory characteristics like neutrophilic leukocytosis but our patient had a milder illness profile, normal umbilical cord separation and no neutrophilic leukocytosis, which made diagnosis difficult and delayed the identification of an underlying immunodeficiency. At our tertiary care center, total 17 cases of LAD have been reported in last 3 years but this case is a very rare variant of leukocyte adhesion deficiency with normal umbilical cord separation, milder skin infection with complete absence of CD18 and normal expression of CD11a, CD11b and 11c and is being reported for the first time as per known literature.

CONCLUSION

This case serves as an important clue for pediatrician about typical sign, symptoms and laboratory investigations may vary in some immunodeficiency variants. However, to gain a deeper understanding of its underlying mechanisms, disease progression and prognosis, further collaborative research across multiple medical centers is essential.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

PATIENT'S CONSENT:

Written informed consent was taken from patient and parents to publish this case report.

AUTHORS CONTRIBUTION

Muhammad Hussain: Conception of the work, drafting and final approval

Mustajab Alam: Critical revision, interpretation of data

Muhammad Zain Arshad, Muhammad Aftab Hussain: Drafting, critical revision

Hina Mushtaq, Maryam Bibi: Interpretation of data

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