

# Antibiotic-Resistant Neutrophilia with Persistent Bleeding: Two Grave Symptoms of Rare Disorder Leukocyte Adhesion Disorder Type III

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## ABSTRACT

Leukocyte adhesion deficiency, Type III (LAD-III) is an unusual autosomal recessive disorder characterised by a disruption in the ability of white blood cells (WBCs) to adhere to blood vessels. This anomaly results in recurrent infections and bleeding complications. The underlying cause of LAD-III is attributed to mutations in the *FERMT3* gene, responsible for encoding the vital protein called kindlin-3. Inside-out signalling of integrins on leukocytes and platelets is disrupted by *FERMT3* mutations and kindlin-3 deficiency in LAD-III. Here, we describe a case of a six-month-old male child from a consanguineous marriage, who presented with progressively increasing anaemia requiring transfusion, low-grade fever, and profuse bleeding post-circumcision. His parents gave a history of recurrent chest infections and cough not responding to antibiotics. The physical examination showed pallor, low-grade fever, and rapid pulse. The blood tests revealed high WBC count with neutrophilia, low haemoglobin, and normal platelet count. The coagulation profile was normal; however, platelet aggregation studies were abnormal showing Glanzmann type pattern with prolonged bleeding time. Bone marrow aspiration and immunodeficiency workup were within the normal limits. Flow cytometry indicated LAD-III (as Type I and II were excluded). This case highlights the importance of considering rare disorders in patients with antibiotic-resistant neutrophilia and persistent bleeding.

**Key Words:** Leucocyte adhesion deficiency, Glanzmann thrombasthenia, Bleeding, Neutrophilia.

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## INTRODUCTION

Leukocyte adhesion deficiency, Type III (LAD-III) is an uncommon hereditary condition that impacts the capacity of white blood cells (WBCs) to adhere to blood vessels, leading to the occurrence of recurrent infections and bleeding issues. Its prevalence is estimated to be approximately 1 in 1,000,000 people, with a higher occurrence observed in individuals of Ashkenazi Jewish ancestry. The underlying cause of LAD-III is attributed to mutations in the *FERMT3* gene, which encodes a crucial protein, called kindlin-3. This protein plays a vital role in activating  $\beta$ -integrins, which are proteins that facilitate the adherence of WBCs to blood vessels. The mutations in *FERMT3* prevent kindlin-3 from activating  $\beta$ -integrins, which leads to the defect in leukocyte adhesion. The symptoms of LAD-III typically appear in early childhood, and present with increased risk for severe bacterial infections, such as pneumonia, meningitis, and sepsis, along with bleeding problems (syndrome of Glanzmann-type), such as easy bruising, nose-bleed, and gum-bleed.<sup>1</sup>

The diagnosis of LAD-III is based on the clinical presentation and the results of genetic testing. Genetic testing is used to confirm the diagnosis of LAD-III. While a cure for LAD-III remains elusive, there are few treatment options available to effectively manage the symptoms. Children with LAD-III typically receive prophylactic antibiotics to prevent infections. They may also need blood transfusions to treat the bleeding problems. In some cases, haematopoietic stem cell transplantation (HSCT) may be an option for people with LAD-III. The outlook for people with LAD-III varies depending on the severity of the disease. Some people with LAD-III live relatively normal lives, while others may experience more severe complications. The outlook for people with LAD-III who receive early treatment is generally good. With proper treatment, people with LAD-III can live long and healthy lives.<sup>2</sup>

## CASE REPORT

A six-month male child, born from a consanguineous marriage, presented with progressively increasing anaemia requiring transfusion (100 ml, RCCs twice) and low-grade fever, relieved temporarily with antipyretics. He also experienced profused bleeding post-circumcision without any significant history of spontaneous bruises, petechiae and ecchymosis previously. He also had a history of recurrent chest infections and cough not responding to broad-spectrum antibiotics. His general physical examination revealed pallor, low-grade fever of 100°F and rapid

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pulse. His systemic examination revealed basal crepitations bilaterally.

His blood tests revealed high WBC count of  $63.5 \times 10^9$  with neutrophilia (neutrophils 66%), low haemoglobin of 5.6 g/dL, and normal platelet count. However, no abnormal cell was reported. Considering the significant history of bleeding post-circumcision and normal platelet count, coagulation profile (prothrombin time [PT], activated partial thrombin time [APTT] and Factor XIII deficiency screening) was advised, which was normal. Bleeding time (BT) was evaluated by Ivy method and was >15 minutes (Normal: 2-9 minutes). Platelet aggregation with platelet-rich plasma (PRP) was done, which revealed a pattern consistent with Glanzmann thrombasthenia (no response with collagen, ADP and epinephrine, and normal response with ristocetin). However, the presence of persistent neutrophilia despite prolonged broad-spectrum antibiotic cover confused the diagnosis. The bone marrow aspiration revealed a marrow with normal cellular composition. The basic primary immunodeficiency work-up indicated normal lymphocyte subset and immunoglobulin levels. Flow cytometry revealed more than 95% of neutrophils that expressed CD18, CD11a, and CD11b integrins. The clinical findings of prolonged bleeding after circumcision, bruises, persistent culture positive infections not responding to broad-spectrum antibiotics, and laboratory findings of persistent neutrophilia, and platelet aggregation studies showing pattern of Glanzmann thrombasthenia, were consistent with the diagnosis of LAD-III.

## DISCUSSION

LAD syndrome is a group of congenital immune disorders characterised by impaired leukocyte activation and adhesion, resulting in the inability of leukocytes to effectively migrate to sites of tissue injury. There are three distinct types of LAD identified: LAD Type I (LAD-I), caused by deficient or absent  $\beta(2)$ -integrins due to mutations in the *ITGB2* gene; LAD Type II (LAD-II), caused by impaired fucosylation of selectin ligands and defective selectin binding and signalling due to defects in the *SLC35C1* gene; and LAD Type III (LAD-III), caused by the absence of kindlin-3, a cytoplasmic protein that cooperatively activates  $\beta 1$ ,  $\beta 2$ , and  $\beta 3$  integrins with TALIN-1, due to mutations in the *FERMT3* gene. LAD-III presents with bleeding similar to that seen in Glanzmann thrombasthenia and platelet dysfunction, in addition to impaired leukocyte adhesion.<sup>3</sup>

Saulter *et al.* conducted a study revealing that 71% of reported LAD-III cases exhibited mucocutaneous bleeding, a characteristic feature of the disease. The severity of the bleeding phenotype in LAD-III might surpass that of Glanzmann thrombasthenia, with reported occurrences of intracranial haemorrhage, gastrointestinal bleeding, and pulmonary bleeding in 15, 15, and 6% of patients, respectively.<sup>3</sup>

In India, an extensive study conducted by Priyanka *et al.* identified LAD-III in five patients who exhibited classical symptoms, including recurrent infections of the skin, ears, and mucosal

surfaces, as well as bleeding from the gums and skin. The age of diagnosis and presentation showed notable variations among the patients.<sup>4</sup>

In a study carried out by Saba *et al.* in Pakistan, a new homozygous stop codon variant c.C286T (p.Q96\*) in the *FERMT3* gene was discovered in a Pakistani family with LAD-III. Additionally, genetic mutations in *FERMT3* were observed in Turkish and Maltese patients, with Turkish patients exhibiting a homozygous nonsense mutation (R509X) and the Maltese patient showing homozygosity for an A-to-G substitution in exon 14 at the splice acceptor site.<sup>5</sup>

Leukocyte adhesion deficiencies, particularly LAD-III, are relatively uncommon worldwide, with LAD-1 being the most frequently diagnosed form (323 cases). LAD-III gives the impression of occurring sporadically, and there is the likelihood that LAD cases are underreported due to the difficulties in accurately diagnosing this rare condition.<sup>6</sup>

It is crucial to recognise that leukocyte adhesion deficiencies are often not considered in clinical practices and are infrequently documented in the scientific literature. As a result, they are underdiagnosed, largely due to the limited utilisation of genetic testing for such rare conditions. Raising awareness among the healthcare professionals and promoting genetic testing can help improve early diagnosis and management of patients with leukocyte adhesion deficiencies.

## PATIENTS' CONSENT:

Informed consent was obtained from the parents of the patient to publish the data concerning this case.

## COMPETING INTEREST:

The authors declared no competing interest.

## AUTHORS' CONTRIBUTION:

SF: Seeing and diagnosing the patient, drafting the manuscript, and critical review.

AM: Critical review, approval of the final version to be published.

RG, NS: Drafting the manuscript, critical review.

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