Leukocyte Adhesion Deficiency Type 1 in a Neonate Presenting with Delayed Umbilical Cord Separation and a Non-healing Inguinal Ulcer: A Case Report

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Abstract

Background: Leukocyte adhesion deficiency type 1 (LAD-1) is a rare autosomal recessive primary immunodeficiency caused by defects in the *ITGB2* gene encoding the β2-integrin subunit CD18 affecting 1 in a million people worldwide. Defective leukocyte adhesion and migration into infected tissues result in recurrent bacterial infections, impaired wound healing, absent or minimal pus formation, and delayed separation of the umbilical cord. Marked leukocytosis, particularly neutrophilia, is an important laboratory clue.

Case Presentation: We report a male neonate who presented at 27 days of life with fever, excessive crying, a non-healing right inguinal ulcer, and failure of the umbilical cord to separate. He was born at 41+2 weeks of gestation by LSCS with a birth weight of 3200 g following an uneventful antenatal and immediate postnatal period.

The infant was exclusively breastfed. On evaluation, the umbilical cord remained attached and the inguinal ulcer showed poor local inflammatory response without significant pus formation. Laboratory investigations revealed marked leukocytosis with a total leukocyte count of 96,800/mm³ and an absolute neutrophil count of 82,280/mm³. C-reactive protein was positive, and blood culture grew coagulase-negative *Staphylococcus*. During hospitalization, the infant developed respiratory distress requiring CPAP, with radiological evidence of pneumonia. In view of the combination of delayed cord separation, severe neutrophilic leukocytosis, non-healing ulcer, and poor pus formation, a primary leukocyte adhesion defect was suspected. Flow cytometric evaluation demonstrated profoundly reduced expression of CD18 (0.00%) and markedly reduced CD11a expression (0.10%), supporting the diagnosis of LAD type 1.

Conclusion: LAD-1 should be considered in neonates presenting with delayed umbilical cord separation, recurrent or persistent bacterial infections, impaired wound healing, minimal pus formation, and unexplained marked neutrophilic leukocytosis. Early recognition and flow-cytometric assessment of β2-integrin expression can facilitate diagnosis and appropriate referral for definitive management.

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Keywords: Leukocyte adhesion deficiency, LAD-1, CD18, β2 integrin, delayed cord separation, neonatal immunodeficiency, neutrophilia, non-healing ulcer

Introduction

Leukocyte adhesion deficiency (LAD) comprises a group of rare inherited disorders characterized by defective leukocyte adhesion and migration from the circulation into sites of infection. Among these, LAD type 1 is the most frequently recognized form and results from quantitative or qualitative defects of the β2-integrin complex. The β2-integrin family includes CD11/CD18 heterodimers expressed on leukocytes. The CD18 subunit is shared by several β2-integrins and is essential for firm adhesion of leukocytes to vascular endothelium and subsequent transmigration into tissues. Deficiency or severe reduction of CD18 therefore

results in impaired recruitment of neutrophils to sites of infection despite profound circulating neutrophilia.

Classical clinical manifestations include delayed separation of the umbilical cord, recurrent bacterial infections, severe periodontitis, impaired wound healing, and absence or marked reduction of pus formation. Neonatal presentation may be particularly challenging because the initial manifestations can mimic severe bacterial infection or other congenital immunodeficiency disorders.

We present a neonate with LAD type 1 who presented with delayed umbilical cord separation, a persistent non-healing inguinal ulcer, severe neutrophilic leukocytosis, and bacterial infection.

Case Presentation

A male neonate was admitted at 27 days of life with complaints of fever, excessive crying, a non-healing ulcer over the right inguinal region, and failure of separation of the umbilical cord.

The infant was born at 41+2 weeks of gestation by lower-segment caesarean section with a birth weight of 3200 g. The antenatal period was reportedly uneventful. The mother was a 29-year-old primigravida with a non-consanguineous marriage.

A lesion over the right inguinal region was first noticed around 7–8 days of life. The lesion persisted and failed to heal. Despite the persistent ulcerative lesion, there was no significant purulent discharge.

At admission, the infant weighed 4.1 kg. Examination revealed an attached umbilical cord with delayed separation and a non-healing ulcer over the right inguinal region. The infant subsequently developed respiratory distress requiring CPAP support. Chest radiography was suggestive of pneumonia.

The combination of delayed cord separation, persistent skin ulceration, severe leukocytosis, and poor pus formation raised suspicion of an underlying primary immunodeficiency, particularly a disorder of neutrophil adhesion and migration.

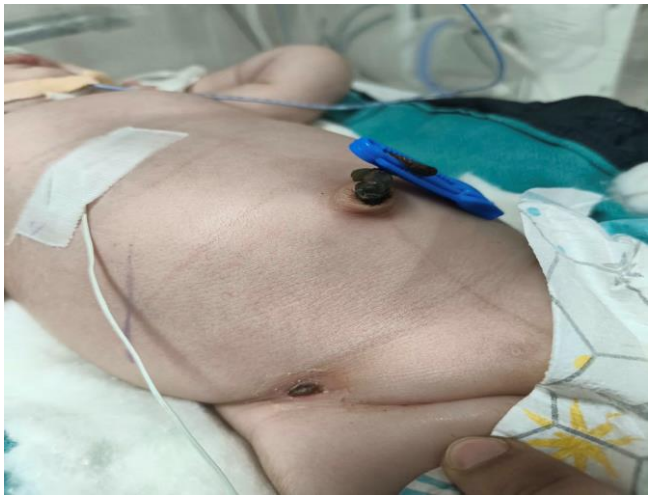

Fig 1: Clinical photograph of the intact umbilical cord and non-healing right inguinal ulcer.

Investigations

- **Initial complete blood count revealed:**

Table 1

Parameter	Result
Hemoglobin	10.4 g/dL
Total leukocyte count	96,800/mm³
Absolute neutrophil count	82,280/mm³
Absolute lymphocyte count	11,616/mm³

Peripheral blood smear showed marked leukocytosis with a predominantly neutrophilic picture, with normocytic normochromic red blood cells.

C-reactive protein was positive.

Blood culture grew coagulase-negative *Staphylococcus*.

The infant was evaluated for an underlying disorder of leukocyte function because of the striking discrepancy between the severe circulating neutrophilia and the relatively poor local inflammatory response at the site of infection.

Flow cytometric evaluation of leukocyte adhesion molecules demonstrated:

- CD18: 0.00%
- CD11a: 0.10%

The profound reduction of CD18 expression, together with the clinical phenotype, was consistent with Leukocyte Adhesion Deficiency type 1.

Diagnostic Reasoning

The diagnosis was considered based on the characteristic combination of:

1. Delayed separation of the umbilical cord
2. Severe persistent neutrophilic leukocytosis
3. Non-healing skin ulcer
4. Minimal/poor pus formation
5. Bacterial infection
6. Profoundly reduced CD18 expression on flow cytometry

In LAD-1, circulating neutrophils are unable to effectively adhere to vascular endothelium and migrate into infected tissues. Consequently, neutrophils accumulate in the bloodstream, producing marked leukocytosis, while the infected tissue demonstrates an inadequate neutrophilic response.

The flow-cytometric demonstration of virtually absent CD18 expression strongly supported the diagnosis of severe LAD-1.

Treatment and Clinical Course

The infant was initially managed for suspected bacterial infection and respiratory distress which was managed with CPAP support. The infant subsequently improved clinically and was maintaining respiratory status in room air.

At the latest clinical assessment, the infant was active and alert, receiving full mother's breast milk feeds. Following the diagnosis of LAD-1, the family was counselled regarding the nature of the primary immunodeficiency, susceptibility to recurrent infections, and the need for specialist immunology/hematology follow-up and evaluation for definitive therapy.

Discussion

LAD-1 is an inherited disorder of leukocyte adhesion caused by defects involving the β2-integrin pathway. The β2-integrin complex consists of a common CD18 β-chain paired with different CD11 α-chains. These molecules are critical for firm leukocyte adhesion and subsequent migration across the vascular endothelium.

During a normal inflammatory response, neutrophils undergo a sequence of events consisting of tethering and rolling, activation, firm adhesion, and diapedesis. Selectins mediate the initial rolling interaction, while β2-integrins, particularly CD11/CD18 complexes, are essential for firm adhesion. Following adhesion, neutrophils migrate through the endothelial layer toward the site of infection.

In LAD-1, defective β2-integrin expression or function prevents effective firm adhesion and tissue migration. As a result, neutrophils remain within the circulation, leading to marked peripheral neutrophilia. However, despite the high circulating neutrophil count, relatively few neutrophils reach the infected tissue. This explains the characteristic combination of extreme leukocytosis with minimal pus formation.

Delayed separation of the umbilical cord is one of the classical clues to LAD-1. Normally, separation of the cord involves an inflammatory process with leukocyte infiltration. Impaired leukocyte migration can therefore result in prolonged attachment of the umbilical cord.

The present case is particularly notable because the clinical presentation occurred during the neonatal period with multiple characteristic findings occurring together. The persistent inguinal ulcer, delayed cord separation, severe neutrophilic leukocytosis, and poor local pus formation provided important clinical clues toward LAD.

The differential diagnosis of marked neonatal leukocytosis includes severe bacterial infection, congenital infections, leukemoid reactions, hematological malignancy, and other primary immunodeficiencies. However, the presence of delayed cord separation and poor pus formation should prompt consideration of LAD.

Flow cytometry is a valuable diagnostic investigation because it allows assessment of surface expression of CD18 and the associated CD11 molecules. In severe LAD-1, CD18 expression may be absent or profoundly reduced. In this infant, CD18 expression was 0.00%, providing strong laboratory support for the diagnosis.

Genetic confirmation through identification of a pathogenic variant in the ITGB2 gene can further establish the molecular diagnosis and is useful for genetic counselling and family planning. Where available, genetic testing should therefore complement immunophenotyping.

Definitive management of severe LAD-1 may require hematopoietic stem cell transplantation (HSCT). Until definitive therapy, prevention and aggressive treatment of infections, appropriate antimicrobial therapy, wound care, nutritional support, and multidisciplinary follow-up remain important.

Learning Points

1. Delayed separation of the umbilical cord is an important clue to primary immunodeficiency.
2. Marked neutrophilic leukocytosis with poor pus formation should raise suspicion of LAD.
3. In LAD-1, the apparent paradox of severe peripheral neutrophilia with poor tissue inflammation results from defective neutrophil adhesion and migration.
4. A persistent non-healing skin lesion with minimal purulent response in a neonate should prompt evaluation of neutrophil function.
5. Flow cytometry for CD18/CD11 expression is an important diagnostic investigation for suspected LAD-1.
6. Profoundly absent CD18 expression, as demonstrated in this infant, is highly suggestive of severe LAD-1 in the appropriate clinical setting.
7. Early recognition is important because severe LAD-1 carries a high risk of recurrent and potentially life-threatening bacterial and fungal infections and may require definitive treatment with HSCT.

Conclusion

This case highlights the importance of recognizing the characteristic clinical phenotype of LAD-1 in the neonatal period. The combination of delayed umbilical cord separation, non-healing skin ulceration, poor pus formation, bacterial infection, and marked neutrophilic leukocytosis should prompt evaluation for a leukocyte adhesion defect. In this neonate, profound absence of CD18 expression on flow cytometry established strong laboratory evidence for LAD-1. Early diagnosis allows appropriate infection management, genetic counselling, immunology referral, and consideration of definitive hematopoietic stem cell transplantation.

Declarations

Ethics Approval and Consent

Written informed consent should be obtained from the parents/legally authorized representative for publication of the case and any accompanying clinical images.

Consent for Publication

Parental consent should be obtained for publication of the patient's clinical details and photographs, where applicable.

Conflict of Interest

The authors declare no conflict of interest.

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Author Contributions
Dr. Ashish Dutta contributed to the clinical evaluation, diagnostic work-up, literature review, and preparation of the manuscript. Dr. Ravi Parihar and Dr. Ahaan Nargotra contributed to clinical evaluation, management, and review of the manuscript. All authors approved the final manuscript.

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