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Case Report

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A fatal yet salvageable inborn error – leukocyte adhesion deficiency

Abstract

Leukocyte adhesion deficiency (LAD) Type 1 is a rare inborn error in infants characterized by delayed umbilical cord detachment, non-healing ulcers, and leukocytosis. Initially, knowledge of LAD was limited to the impairment of granulocyte function due to the scarcity of cases. However, as more and more cases are being reported, the knowledge of the bio-physiology of white blood cells, platelets, and various intercellular reactivity and signaling provides a new perception of this disease. We present a 17-day-old female child who presented with complaints of fever and redness in the perianal region and popliteal fossa. Investigations showed leukocytosis in blood and cerebrospinal fluid (CSF), raised C-Reactive Protein (CRP), and Pseudomonas-positive blood and CSF culture. Flow cytometry revealed the absence of CD18, CD11a, and CD11c. Aggressive antimicrobial agents were started; however, the baby died on day 30 of life. In this report, we emphasize the essential investigations needed for early diagnosis and effective precautions through which we can decrease the fatality rate of this rare disorder.

Keywords: delayed cord detachment, flow cytometry, leukocyte adhesion deficiency, leukocytosis, non-healing ulcers

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Introduction

In healthy individuals, inflammation is a necessary process to eliminate pathogens, and this is dependent on the effective migration of leukocytes to the target sites. Cell adhesion molecules such as Selectins and Integrins carry out this process of neutrophil extravasation from the bloodstream. Defects in the genes and functioning of specific leukocyte Beta 2 (CD18 chain) Integrins and their corresponding glycoproteins (CD11a, CD11b, CD11c, etc.) lead to the clinical syndrome of Leukocyte Adhesion Deficiency (LAD).[1]

Leukocyte adhesion deficiency (LAD) is a group of rare autosomal recessive inherited disorders[2] so rare that, to date, about 300 cases of LAD-1 have been reported worldwide.[3] It is characterized by immune deficiency and peripheral neutrophilia.[2] Although leukocytes are present in the bloodstream, they are unable to migrate from the bloodstream toward sites of tissue injury. Due to the scarcity of cases, knowledge of LAD was limited to the impairment of granulocyte function. However, as more and more cases are reported, the knowledge of the bio-physiology of white blood cells, platelets, and various intercellular reactivity and signaling provides a new perception of this disease.[4] There are three types of LAD syndromes, with Type 1 being caused due to defects in the Beta 2 integrin family, Type 2 caused by a defect in the ligands of Selectin molecules,[3] and Type 3 due to kindlin-3 protein defect affecting cell adhesion as well.[5] These syndromes can present with a variety of infectious presentations, including omphalitis, periodontitis, osteomyelitis, meningitis, and so on.[6] Infectious foci characteristically are non-purulent and eventually become necrotic because of abnormal wound healing.[2] Here, we describe a case of LAD-1, who presented with classic symptoms and succumbed within one month of life, even after aggressive management.

Case profile

A 17-day-old girl child presented to the emergency department with complaints of fever and redness at the perianal and right popliteal fossa region with restricted right lower limb movements. Additionally, on examination, the umbilical cord had not yet separated (Day 17). On further inquiry, the baby was full-term, was born through normal vaginal delivery, cried immediately after birth, and weighed 4kg at birth.

The baby was admitted, and primary treatment with evaluation for septic screening was done.

Investigations revealed raised WBC count in blood and CSF and raised CRP. Blood and CSF cultures were Pseudomonas species positive. Despite high-level intravenous antimicrobial treatment (meropenem, piperacillin, vancomycin, colistin, and antifungals), blood reports showed persistent leukocytosis - the white blood cell count was above one lakh, and even after regular wound dressings, the patient had a non-healing ulcer over her right popliteal fossa and perianal region (Figure 1).

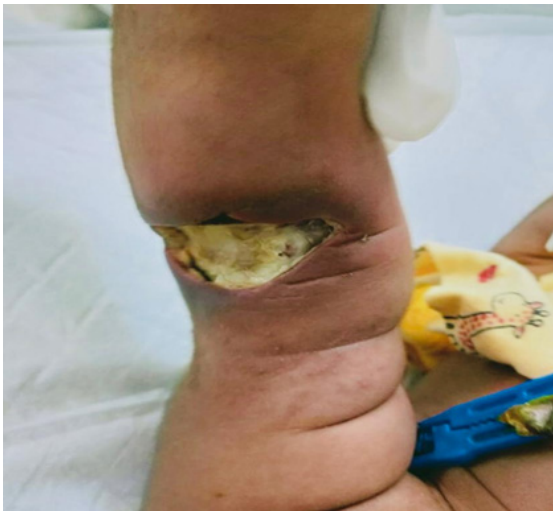

Figure 1 Non-healing ulcer on right popliteal region.

The baby was suspected of having Leukocyte Adhesion Deficiency, and flow cytometry was done, which revealed a complete absence of CD18 (b2-integrin), CD11b, and CD11c on granulocytes. This

confirmed the diagnosis of type 1 LAD (Figure 2). Unfortunately, even after best efforts, the baby expired on day 30th of her life.

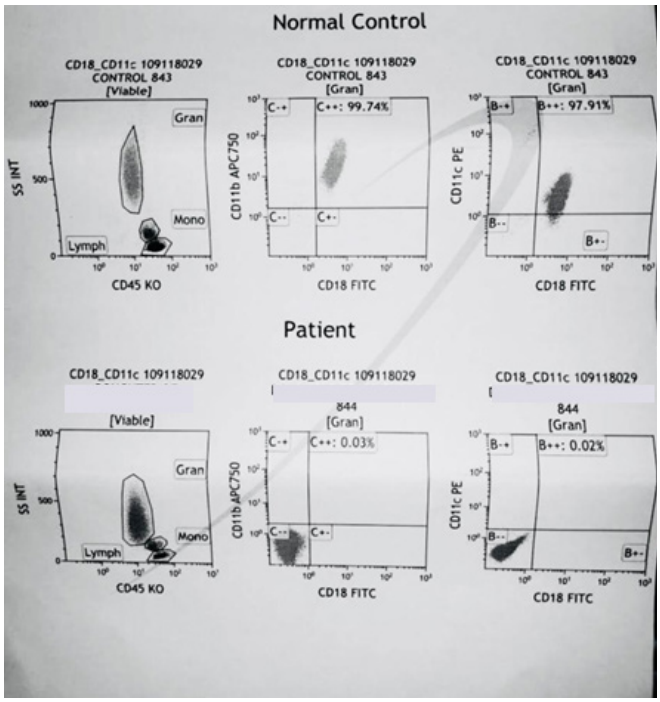

Figure 2 Flow Cytometry: a complete absence of CD18 (b2 integrin), CD11b, and CD11c on granulocyte.

Discussion

Leukocyte Adhesion Deficiency (LAD) syndromes are classified into three sub-types depending on the clinical features and flow cytometry results.[6] To make the correct diagnosis, the initial step is clinical suspicion which includes a history of delayed cord detachment, non-healing ulcers, recurrent infections, a persistently elevated White Blood Cell count, and a confirmation by flow cytometry.[4]

In the present case, all the characteristic signs were present to confirm the diagnosis. The baby presented with a non-healing wound over the popliteal fossa, persistent leukocytosis [WBC >1lacs/cumm – 85% neutrophils], and a delay in umbilical cord separation. In addition, the blood culture confirmed the presence of pseudomonas infection, and on flow cytometry, there was a complete absence of CD18, CD11b, and CD11c molecules on granulocytes.

Although a definitive cause for LAD-1 is not established, Strickler et al.[2] reported a case of LAD-1 associated with CMV infection-related developmental delay, functional defect of β2 integrins, presence of CD18 antigen, and high consanguinity. They concluded that congenital infections and genetic factors like consanguinity are associated with LAD- 1, which with timely and efficient primary health interventions can be prevented. However, in the present case, there was no history of consanguinity, the antenatal period was uneventful, and the parents belonged to middle-class socio-economic status suggesting that the factors mentioned by Strickler et al. associated with LAD-1 are not limited to congenital infections, genetic and psychological factors only and that knowledge of the disease still needs to be refined.

Recently, Harris et al.[5] discussed the deficient expression of β2 integrin subtypes: aLβ2, aMβ2, aXβ2, aDβ2 and newly discovered β2 integrin-dependent actions like adhesion and signaling of polymorphonuclear leukocytes and monocytes in the pathophysiology of LAD-1 patients.[5] These insights will help broaden our understanding of the molecular interactions and approach to diagnosing the various types of LAD syndromes.

Kambli et al.[7] did a multicentric study on 127 cases of LAD-1 and gave a brief classification based on the expression of CD18 on neutrophils: mild (>30%), moderate (2%-30%), and severe (<2%). Table 1 is formulated from their studies and includes the median age at presentation, diagnosis, and mortality in different categories.

Table 1 This study also proves that diagnostic accuracy increases after adding the CD11a marker

Lad 1	Median age of presentation	Median age of diagnosis	Mortality (survival more than 2 years)
Mild	2.5 months	84 months	60%
Moderate	1 month	5 months	16%
Severe	0.3 month	3 months	6%

Gorjipour et al.[8] reported a case series and review of literature on five patients of LAD-1 ranging from the age of one month to ten years and concluded that for ensuring a definitive diagnosis, early identification is needed and that early implementation of bone marrow transplantation might save the life. Unfortunately, however, the outcome is often not favorable due to life-threatening complications and unavailability of resources,[9] as we have experienced in our case too.

The only current treatment for LAD syndromes is a hematopoietic stem cell transplant. Tokunaga et al.[9] reported a case of a 20-year-old female patient who presented with occasional recurrent life-threatening infections and received successful non-myeloablative bone marrow transplantation. This remarkable feat shows that the severity of the disease is also an important factor in determining survival and success with Bone Marrow Transplantation. Novoa et al. also stated in their review of published LAD cases that hematopoietic stem cell transplant is the only curative option of therapy and without it, for severe cases, there is a limited two-year survival.[10] Therefore, prompt identification of infants with severe or atypical infections, delayed umbilical cord separation, and raised white blood cell counts is necessary to advise proper curative management.

Conclusion

Although Leukocyte Adhesion Deficiency is a rare genetic syndrome, nowadays, due to the availability of diagnostic modules, more and more cases are being diagnosed. To diagnose a case of LAD- 1, we must have a high suspicion when a newborn presents with non-healing ulcers, persistently elevated leukocytes, and delayed cord detachment. Bone marrow transplantation should be done timely once the diagnosis is confirmed by flow cytometry to save the newborn's life.

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Conflicts of interest

The author declares no conflicts of interest.

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