Case Report

Leukocyte Adhesion Defect

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Abstract

Leukocyte adhesion defect (LAD) is a rare, autosomal recessive primary immunodeficiency disorder of phagocytes, in which there is defective aggregation at the site of infection due to the absence of surface integrins. Diagnosis is based primarily on flowcytometric analysis of neutrophils for the surface expression of CD11, CD18 and CD15s. We describe here a case of a 7 months old boy who presented with a characteristic history of recurrent infections, marked leukocytosis and delayed separation of umbilical cord. The diagnosis was established by demonstration of the absence of integrins on the surface of patient's neutrophils by flowcytometric analysis.

Introduction

Neutrophil responses to inflammation are initiated as circulating neutrophils flowing through the postcapillary venules detecting low levels of chemokines and other chemotactic substances released from a site of infection. The initial associations are low affinity, reversible and primarily mediated by cell-selectin-carbohydrate interactions. This leads to the phenomenon known as leukocyte rolling, which allows more intense exposure of neutrophils to activating factors TNF and IL-1, leading to induction of qualitative and quantitative changes in the family of β2 integrin adhesion receptors on the neutrophils (the CD11/CD18 group of surface molecules).[1]

Leucocyte adhesion deficiency is characterized by the inability of leucocytes, especially neutrophils, to emigrate from the blood stream towards sites of inflammation. First patient was described in 1980 by Crowley et al, he had elevated peripheral blood neutrophil count with few neutrophils at the inflammatory site and recurrent infections.[2] Only about 300 cases of LAD I have been reported worldwide.[3] Infectious foci characteristically are non-purulent and eventually become necrotic because of abnormal wound healing. Various molecular defects have been described: LAD 1 is due to mutation in ITGB2 gene on chromosome 21q22.3 that encodes the β2 subunit of integrin molecule.[2] In LAD 2 there is mutation in gene on chromosome 11 that encodes Golgi apparatus GDP-L-fucose transporter.[3-5] The genetic defect of LAD 3 is unknown but there is defect in integrin activation process. More than 300 cases have been described for LAD 1 worldwide, while for LAD 2 and LAD 3; there are less than 10 cases each.[4] FACS (Fluorescence activated cell sorter) analysis of neutrophil surface CD18 and CD15s are diagnostic for LAD I and II respectively. Inability to express/up regulate CD18 on neutrophil surface following phorbol myristate acetate stimulation can be used as an alternative for diagnosing LAD1.[6]

Case Report

A 7 months-old male infant was brought with a history of loose motions for 5 days and abdominal distension for 1 day. There was no history of green colored vomitus or constipation. He had diarrheal episodes since the age of 1 month and every 2-3 weeks it was accompanied with abdominal distension. For these complaints he was hospitalized 3 times prior to this admission. The umbilical cord separated around 45th postnatal day. There was no history suggestive of sepsis or umbilical infection in the neonatal period. He attained social smile by 2 months and had not yet developed head control. He was the 5th child of first degree consanguineous parents born at term by spontaneous vertex delivery following an uncomplicated pregnancy. Two elder siblings died in early infancy (40 days and 3 months of age) due to sepsis and both had history of delayed separation of umbilical cord.

On examination, the infant was febrile with no dysmorphism. His weight was 4100 grams (birth weight was 3000 grams). He appeared pale, no icterus, no lymph node enlargement, no petechiae or bruises. He had stable vital signs. Abdomen was distended with no superficial veins. Umbilicus was central and inverted. The liver was palpable 5 cm below the costal margin, soft in consistency and nontender with smooth surface. The spleen was palpable 4 cm along its long axis below costal margin, soft in consistency, smooth surface and splenic notch wasn't palpable. There was no ascites and bowel sounds were audible. Rest of the systemic examination was normal.

Investigations revealed haemoglobin concentration of 7.8 g/dL, platelet count of 431,000/mm3, total leukocyte count of 78,000/mm^3 with a differential count of neutrophils 94%, lymphocytes 5% and monocytes 1%.Peripheral film showed microcytosis with 1% reticulocytes. No blasts cells were seen. Blood culture did not yield any organism. Serum

electrolytes, renal and liver function tests were normal. Bone marrow examination revealed myeloid hyperplasia with normal maturation, with normal erythropoiesis and megakaryopoiesis. No evidence of malignancy or storage disease was found. Serum immunoglobulin profile revealed IgE 74iu/ml, IgA 139 mg/dL, IgM 340 mg/dL and serum IgG 1580mg/dl, these were normal for the age.

He later developed an ulcer under the chin which despite treatment with intravenous antibiotics became necrosed and spread to the lateral margins of the neck. Later he developed similar areas of necrosis over the left mid thigh, around umbilicus and right ear lobule (Fig I).

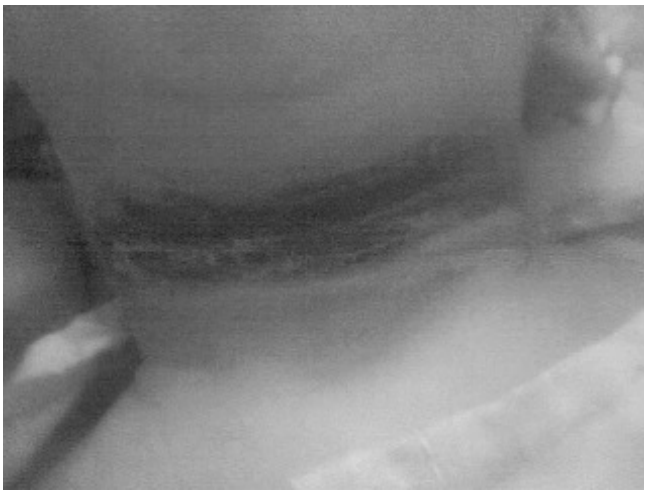

Fig I: Non-suppurative necrotic ulcer over neck.

Antibiotics were changed many times with possible suspicion of Methicillin resistant streptococcus but there was no improvement.

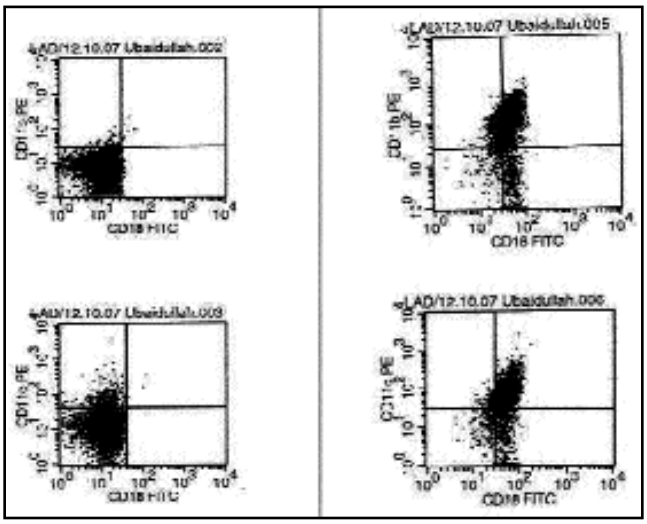

Fig II: Flowcytometric Analysis of CD11a, CD11b and CD18. Left panel shows absence of surface integrins on patient's gated neutrophils. Right panel shows the control.

Flow cytometry was done. Lymphocyte subset analysis revealed slightly raised B cells (2016 cells/ul) but his neutrophils were completely deficient for surface expression of integrins: CD 11b, CD11c and CD18 (Fig II). Based on his clinical presentation, family history and flowcytometric analysis, the diagnosis of leukocyte adhesion defect type 1 was established. However, soon after the diagnosis was made, patient succumbed to disseminating infection and expired.

Discussion

Leukocyte adhesion defect, because of its rarity, presents a diagnostic dilemma. The first step in the accurate diagnosis is clinical suspicion (delayed separation of the cord, infection with pus formation) confirmation requires flowcytometric analysis of leukocytes for the presence of integrins. Although modern flowcytometry studies have facilitated the diagnosis, the practitioners must be aware of the clinical features that point towards this rare entity. The umbilical cord of the newborn usually sloughs by the end of 2nd postnatal week[7] and mean time of separation of umbilical cord is 7.4 days.[8] However, it must be kept in mind that there could be other reasons for delayed separation of the umbilical cord such as urachal anomalies,[9] antibiotic administration, prematurity and low birth weight.[8]

Our patient presented with recurrent infections and later he developed a nonhealing, nonpurulent and necrotic ulcer. There was also a history of delayed umbilical cord separation with family history of a similar ailment.

The differential diagnosis considered were infection with leukemoid reaction, congenital leukaemia, storage disorder, immunodeficiency disorder or congenital infection (TORCH). Serum immunoglobulins and BCG scar formation were normal. Bone marrow examination ruled out haematological malignancy and storage disorder. With the characteristic clinical features of delayed umbilical cord separation, severe infection despite extreme neutrophilia and non-purulent ulcers, it was decided to investigate this child for leucocyte adhesion defects. The absence of CD 11b, CD11c and CD18 on the patient's neutrophils detected by flow cytometry confirmed the diagnosis of LAD 1 in our case.

Our case is interesting due to the fact that there was a history of similar ailments and deaths of infants due to overwhelming infections in two other families related to the patient and settled in the same town. These infants also had delayed separation of the umbilical cord. This could be due to the practice of first cousin marriages perpetuating the disease since LAD is associated with autosomal recessive inheritance.

Only about 300 cases of LAD I have been reported worldwide.[3] Although cases of LAD1 have been reported from all over the world, to our knowledge, this is the first case reported from Pakistan. The aggressive nature of this disease demands prompt diagnosis as aggressive antibiotic therapy to prevent infections can help in waiting period for finding a suitable donor for bone marrow transplant.

Conclusion

The rarity of this disease requires that physicians have a high index of suspicion in a child with history of delayed umbilical cord separation, repeated infections and marked leukocytosis, even in the absence of infections. The diagnosis can be established by flowcytometric analysis of neutrophils surface integrins.

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