CASE REPORT

A PATIENT WITH LEUKOCYTE ADHESION DEFECT

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Abstract

During inflammation, leukocytes play a key role in maintaining tissue homeostasis by elimination of pathogens and removal of damaged tissues. Leukocytes migrate to the site of inflammation by crawling over and through the blood vessel wall, into the tissue. Leukocyte adhesion deficiencies (LAD 1, LAD 2 and LAD 3) are caused by defects in the adhesion of leukocyte to the blood vessel wall due to mutations in the genes encoding $\beta 2$ integrin, selectin and kindling-3, respectively. Patients experience recurrent none pus forming bacterial infections and neutrophilia, often preceded by delayed separation of umbilical cord. This case report describes a child who presented with umbilical sepsis followed by separation of the umbilical cord on day 15, and recurrent bacterial meningitis with high neutrophilia.

Introduction

The cellular elements of the human immune system are constantly communicating with each other. This network includes endothelial surfaces, as well as extra-cellular matrices and leads to modulation of immune and inflammatory responses and control of cell traffic. Some of these interactions depend on cytokines for their regulation, others require firm leucocyte-cell or leucocyte-matrix contact, called adhesion.[1]

Leukocyte adhesion defects (LAD) is a rare group of disorders of leucocyte function transmitted by autosomal recessive pattern of inheritance[2]. LAD syndrome is characterized by delayed umbilical cord separation, recurrent severe bacterial infection, periodontitis, and delayed wound healing and often persistent leukocytosis with absent pus formation. It also causes reduced inflammatory response in spite of a high neutrophil count. There are 3 types, LAD 1, LAD 2 and LAD 3. Here we present a child with severe LAD 1. There are 3 reported cases[3] from Sri Lanka though this is a very rare disease. To our knowledge, this is the fourth case of a child affected with LAD1, reported in Sri Lanka.

Case history

A five-month-old baby girl was admitted with fever and poor feeding over the preceding two days. She was the first born

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to second-degree consanguineous parents, and the antenatal, natal and immediate postnatal periods had been uneventful. Her umbilical stump had fallen on day 15 and she had been treated for umbilical sepsis with intra venous antibiotics for 5 days at the age of 19 days. At the age of 42 days she had been treated for meningitis in another hospital. She had received her routine vaccinations without any complications. Her development was age appropriate and she was thriving reasonably well.

The white cell count on admission was 58 x 10^9/L with 80% neutrophils, and the haemoglobin and platelet counts were normal. The blood film revealed no abnormal cells. C reactive protein was 196 mg/L (<6). The CSF analysis showed features of pyogenic meningitis. She was successfully treated with 21 days of cefotaxime.

In view of the recurrent severe infections she was further evaluated. Her C3 and C4 levels were normal. Nitro blue tetrazolium (NBT) test and immunoglobulin levels, CD3,CD4,CD8 and CD19 were normal. As the child had features of leucocyte adhesion defect and the confirmatory tests were not available in the country, the child was sent to India for confirmation of LAD. The results showed CD18-0.1%,CD11a-0.1%,CD11b-2.3%,CD11c-0.1%, suggestive of severe LAD 1.

Later she presented with another episode of severe sepsis and died in spite of treatment.

Discussion

LAD1 is a rare disorder of immune deficiency that occurs in 1 in 10 million births[2]. Only about 300 cases have been reported worldwide[2].

Patients with LAD present with recurrent and often life threatening infections. *Staphylococcus aureus*, group $\propto/\beta$ hemolytic streptococci, Proteus mirabilis, Pseudomonas auriginosa and E coli are common pathogens[1].

A deficiency in β_2 integrins was recognized to be the cause of this syndrome in the early 1980s.[1] The essential function of the integrins is the integration of the cytoskeleton with the extracellular environment and they are found on most cell types. The $\beta_2$integrins (CD11/CD18), a glycoprotein complex, is required for adhesion dependent function such as aggregation, spreading on artificial substrates, chemotaxis, phagocytosis, cell mediated killing, and adherence to endothelium. Each integrin consists of a distinct heavy (150-180 kDa) $\propto$ polypeptide chain non covalently linked to light (95 kDa) β polypeptide chain (CD18) common to all three sub units: CD11a (lymphocyte function associated antigen-1(LFA-1) present on virtually all circulating leucocytes), CD11b (CR3, Mac-1, Mol, is limited to neutrophils, monocytes and natural killer cells) and CD11c (CR-4,gp 150,95 has a similar distribution to CD11b)[1]. These three types of integrins are responsible for the tight adhesion of neutrophils to the endothelial surface, egressing from the circulation and adhesion to iC3b (inactivated C3b) coated microorganisms, which activate the phagocytosis [4,1].

Monocyte function is also impaired with poor fibrinogen binding function- an activity that is promoted by CD11/CD18 [5,4].

Confirmation of LAD 1 is by flow cytometric measurement of surface CD11b/CD18 in stimulated and unstimulated neutrophils[1]. Patients with severe disease express <2 % of CD 18, whereas patient with moderate disease

express 2-30 % of normal amount of CD 18[6,7]. Definitive diagnosis is based on genetic analysis, revealing mutations on ITGB2[7].

LAD 2 shares all clinical features of LAD1 but patients have normal CD 11/CD 18[8] because this disease is due to a defect in selectin in the vessel wall, which binds with the ligands of neutrophils[9,8]. However, in LAD 2 the intensity of infection is milder than in LAD 1[7]. In addition children with LAD 2 exhibit neurological deficits and craniofacial dysmorphism as well[7], and they lack erythrocyte ABO blood group antigens. LAD 2 is also known as a congenital disorder of glycosylation IIc[4].

LAD 3 shows similar risk of infections as in LAD 1, and is also associated with Glanzmann thrombasthenia like bleeding disorder[5].

Treatment for LAD 1 depends on the phenotype as determined by the expression of CD 11/CD18. Early allogeneic haemopoitic stem cell transplantation is the treatment of choice for severe LAD1 and LAD 3. The mainstay of conservative treatment is antibiotics given during infections and as a prophylaxis. LAD 2 patients have responded to fucose supplementation[9].

Conclusions

LAD is a group of disorders of immunodeficiency characterized by recurrent bacterial and fungal infections. The condition should be suspected in such patients with delayed separation of umbilical stump or umbilical sepsis without pus formation. Persistent, very high white cell counts support the diagnosis.

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