Leukocyte adhesion deficiency type II: Long-term follow-up

Amos Etzioni, MD, Ruth Gershoni-Baruch, MD, Shimon Pollack, MD, and Naim Shehadeh, MD *Haifa, Israel*

Leukocyte adhesion deficiency (LAD) syndromes are characterized by increased incidence of infections, marked leukocytosis, and impaired adherence of neutrophils to endothelial cells.[1] LAD I, first described in 1980, is caused by a defect in the integrin family, specifically in the β-subunit.

More than 150 patients were reported, and they were divided into 2 groups with varying severity of disease: (1) a severe group with no expression of CD18, which is associated with early death unless bone marrow transplantation is performed, and (2) a moderate group with a 2% to 5% expression of CD18, which is associated with much longer life expectancy and recurrent infectious episodes throughout the years.[2]

LAD II has been recently described[3] and is caused by the absence of Sialyl Lewis X (SLeX), a ligand on neutrophils for the selectin family and a major determinant in the first step of the adhesion cascade (i.e., the rolling phase).[4] In our initial report we described the clinical symptoms in our infant patients, and these were somewhat compatible with the moderate form of LAD I.[3] Long-term follow-up for 5 more years showed complete diversion of the clinical course from that reported previously.

CASE REPORT

The patient, currently 10 years of age, has severe mental and growth retardation. His height (90 cm) and weight (12 kg) are much below the third percentile for his age. The child is ambulant, yet his language is null, although he understands simple commands. He is totally dependent and is not toilet trained. In the last 3 years, he had 2 convulsive episodes. During a varicella infection, he had cerebellitis, which resolved completely. His skin lesions during the varicella episode were not superimposed with bacterial infection and disappeared after 4 to 5 days as expected for normal children. During the years, he did not have serious infections, including pulmonary infections. The several times that he had a fever, it was caused by viral infections that resolved spontaneously. He does not need prophylactic antibiotics, and does not have skin infections or abnormal skin healing. His only medical problem is severe persistent periodontitis (Fig. 1). Repeated laboratory studies that were performed when the child was free from any infection showed leukocytosis (white blood cell count, 39,500 with 75% neutrophils and 20% lymphocytes). SLeX (CD15s) expression, measured by flow cytometry, remains consistently very low (i.e., only 2% to 3% of the control value).

Abbreviations used
LAD: Leukocyte adhesion deficiency
SLeX: Sialyl Lewis X

DISCUSSION

Although in LAD I all the clinical symptoms can be related to the adhesion defect, LAD II has a broader range of symptoms affecting several organs. We believe that this is because of the primary defect, which is a general defect in fucose metabolism resulting from a genetic mutation in an enzyme converting GDP mannose to GDP fucose (Etzioni et al., unpublished data). This deficiency contributes, in a yet unclear way, to impaired growth and brain development and is responsible for the severe growth and mental retardation observed in our patient.

Surprisingly, the child did not have an increased incidence of infection while growing up, although as an infant he had several episodes of pneumonia. This unusual observation can be partly explained by the fact that other immune mechanisms have matured to compensate for the defect. Alternatively, one can speculate on the importance of the selectin family in the normal host response. Moreover, the 2% to 3% expression of SLeX may also contribute to the milder form of disease, as is seen in the moderate form of LAD I.

Recently, knockout mice that lack one or more of the selectin molecules were generated, and they too show no increase in spontaneous infections.[5] Although impaired host defense against systemic infections was observed in E-selectin– or P-selectin–deficient mice, they were not as severe as those seen in CD18 knockout mice.[6] Knockout mice with a deficiency of α(1,3)fucosyltransferase FucTVII, and thus lacking SLeX, showed very similar patterns as those seen in our patient.[7] Although severe impairment in leukocyte adhesion was found, the mice were free of microbial infection and did not develop the spontaneous bacterial dermatitis exhibited by the P-selectin and E-selectin double deficient mice.[6] Still, one should be cautious not to draw conclusions when comparing knockout mice with rare cases of human "experiments of nature."

Severe impairment in migration of neutrophils to the skin from LAD II similar to that observed in LAD I was

From the Department of Pediatrics and Clinical Immunology, Rambam Medical Center, B. Rappaport School of Medicine, Technion, Haifa.
Reprint requests: Amos Etzioni, MD, Department of Pediatrics, Rambam Medical Center, Haifa, Israel 31095.
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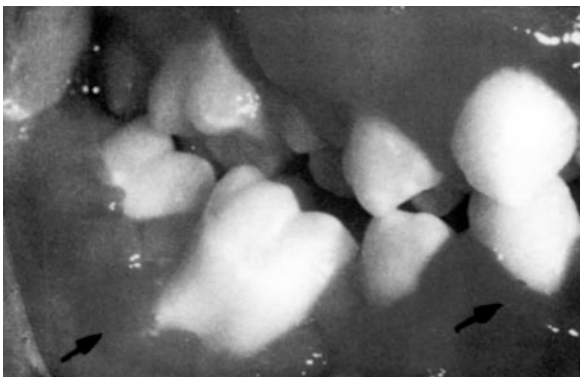

FIG. 1. Severe persistent periodontitis in a child with LAD II.

described,[8] yet no impairment in wound healing was seen in our patient. We have recently reported on a defect in lymphocyte homing to the skin in LAD II.[9] Lymphocyte homing to the skin depends on the presence of the cutaneous lymphocyte antigen, a molecule that also contains fucose and is thus deficient in LAD II.[10] Indeed, a marked impairment in delayed-type hypersensitivity response in the skin was found in the patient.[9] Still, no skin problems that can be related to such a defect were observed, and the clinical course during the varicella disease was completely normal.

Thus the only clinical symptoms that persisted throughout the years was severe periodontitis, which is also very common in LAD I. We believe that further basic and clinical studies should be done to clarify the role of the selectin family in the normal host immune response.

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