A child with chronic generalized lymphadenopathy and splenomegaly diagnosed as Autoimmune Lymphoproliferative Syndrome (ALPS)

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Abstract

Autoimmune Lymphoproliferative Syndrome (ALPS) is a scarce disorder caused by mutations in the FAS *gene in about 75% of cases, characterized by immune dysregulation due to disrupted lymphocyte homeostasis. The disease is characterized by accumulation of double negative (CD3+ CD4- CD8-) T cells (DNT) in the peripheral blood. We describe a case and review the literature.*

Keywords: Autoimmune lymphoproliferative syndrome, apoptosis, lymphocyte homeostasis, FAS, Cytopenia. Double negative T cells.

INTRODUCTION

Autoimmune lymphoproliferative syndrome (ALPS) is a variable clinical

condition that has very low incidence. The exact prevalence is still unknown (1). It an inherited lymphoid disorder which results from mutations in molecules involved in the *Fas-Fas* ligand pathway (2). ALPS is the first human disease whose etiology has been attributed to a primary defect in apoptosis or programmed cell death. Awareness of this disease is important as the differential diagnosis includes common autoimmune disorders such as autoimmune hemolytic anemia and immune thrombocytopenia. In a recent retrospective analysis of children with Evan's syndrome, 58% were found to have ALPS (3). Lymphoproliferation is the most common clinical manifestation in ALPS accompanying with lymphadenopathy, hepatomegaly, or splenomegaly (4)

In 1967, five patients with lymphadenopathy, splenomegaly, and autoimmune cytopenia have been diagnosed as malignant lymphoma with similar characteristics by Canale and Smith (5) and named as Canale-Smith syndrome.

CASE REPORT

9 years old boy,7th child of consanguineous marriage, presented with Fever and sore throat 1 week duration. Physical examination was remarkable for pallor, generalized lymphadenopathy and hepatosplenomegaly (3 and 5 cm respectively). Laboratory evaluation showed Hemoglobin: 10g/dl, WBC count: 4.5x103/µL, neutrophil count: 2000, platelets: 94,000/mm3, Coagulation

profile: normal, ESR:70, ASOT:799.Peripheral blood smear showed microcytic hypochromic picture with mild poikilocytosis and anisocytosis.RBCs showed rouleaux formation.WBC showed few atypical lymphocytes. No blast cells. Platelets showed thrombocytopenia with few giant cells. Serum immunoglobin levels low. Flow cytometry showed (CD3: 2772, CD4:1588, CD8:984). Peripheral blood lymphocytes were analyzed by flow cytometry for double negative T cells (CD3+ CD4-CD8-DNT). Abdominal ultrasound revealed hepatosplenomegaly. A cervical Lymph node biopsy done twice while first one revealed chronic suppurative granulation inflammation consistent with TB. The second sample showed caseating granulation reactions, microbiological study failed to isolate organism. Tuberculin test is negative. BCG scar present.

The patient was diagnosed to have ALPS on the basis of (*i*) lymphadenopathy with splenomegaly, (*ii*) non specific lymph node hyperplasia and preserved architecture, (*iii*) raised circulating double negative T cells, (iiii) gene study.

Discussion

ALPS should be suspected in children presenting with autoimmunity and lymphadenopathy. Investigation should include flow cytometric analysis of peripheral blood to look for CD3+ DNT cells and ideally a test for apoptosis (diagnostic criteria – *Table I*). However, demonstration of defective antigen induced apoptosis in cultured activated lymphocytes *in vitro* requires adequate laboratory support and significant cost.

Lymphoproliferative disease in ALPS does respond to corticosteroids and other immunosuppressants, but symptoms recur upon dose reduction, and long-term side-effects outweigh benefits unless lymphoproliferation is causing critical obstructive disease. Advice concerning splenic rupture and avoidance of contact sports is recommended. Autoimmune cytopathies also respond well to corticosteroids and short courses of high dose treatment have been more effective at controlling these conditions. Immune thrombocytopenia is less sensitive to intravenous immunoglobulin therapy than conventional idiopathic thrombocytopenia purpura (Rieux-Laucat et al, 2003b).

ALPS patients have an increased risk of secondary malignancies. The risk is approximately 10–20 % and is most prevalent in FAS mutant ALPS (6). Other autoimmune manifestations including autoimmune nephritis, hepatitis, gastritis, arthritis, and uveitis are infrequently observed (7).

TABLE I DISEASE DEFINITION AND CLASSIFICATION OF ALPS(1)

Required feature

- Chronic nonmalignant lymphoproliferation ± splenomegaly
- Raised (>1%) circulating DNT cells
- Defective antigen induced apoptosis in cultured activated lymphocytes *in vitro*

Supportive features

- Autoimmune disease
- Positive family history of ALPS
- Characteristic lymph node or splenic histology*
- Mutation in gene coding for Fas

ALPS classification

- Ia - TNFRSF6 mutation
- Ib - Fas ligand gene mutation
- II - Caspase 8 or 10 gene mutation
- III - Unknown genetic cause

*Where identification of FasL, caspase 8 and caspase 10 mutations is not available, ALPS is more practically classified as type Ia or type non-Ia. *Architectural preservation, florid reactive follicular hyperplasia and marked paracortical expansion with immunoblasts and plasma cells*(9)

Lesson

Timely recognition of Autoimmune Lymphoproliferative Syndrome (ALPS) and appropriate therapy might improve the patient outcomes.

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