

CASE REPORT

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Autoimmune Lymphoproliferative Syndrome (ALPS) in a Boy with Massive Lymphadenopathy

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ABSTRACT

Autoimmune lymphoproliferative syndrome (ALPS) is an uncommon nonmalignant lymphoproliferative disease which is characterized by chronic, persistent or recurrent lymphadenopathy, splenomegaly, hepatomegaly, immune cytopenia, hypergammaglobinemia and increased risk of lymphoma.

We report a 2-year old boy with hepatosplenomegaly as first presentation. Petechial and purpuric rashes with massive cervical lymphadenopathies developed 10 months later. In laboratory tests anemia, thrombocytopenia and hypergammaglobinemia were observed. According to flow cytometry increased double negative T cells and by apoptosis assay decrease apoptosis of lymphocytes accompanied clinical manifestations, thus diagnosis of ALPS was established.

In conclusion; in all patients with massive lymphadenopathy and hepatosplenomegaly; especially with cytopenia; ALPS should be considered.

Key words: Autoimmune Lymphoproliferative Syndrome; Apoptosis; Cytopenia

INTRODUCTION

Autoimmune lymphoproliferative syndrome is a rare disease due to an impaired apoptosis. This condition leads to the accumulation of polyclonal population of

T cells (double negative T cells or DNT cells) which express CD3 as well as α/β antigen receptors and do not have CD4 or CD8 markers. Also defective B cell apoptosis and increased survival of autoantibody-producing B cells accompanying high interleukin-10 levels cause hypergammaglobinemia.¹⁻⁷ There are three criteria for diagnosing this syndrome: I: Chronic nonmalignant lymphoproliferation (e.g. chronic splenomegaly and polyadenopathies). II: Defect in lymphocyte apoptosis in vitro. III: $\geq 1\%$ double

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negative α/β + T cells (α/β + CD4-CD8- T cells) in peripheral blood or presence of DNT cells in lymphoid tissue.^{1,8}

CASE PRESENTATION

Our patient was a 2-year old boy weighting 11 kg when he was evaluated for protrusion of the abdomen. His problem started 5 months ago and gradually progressed. He was an offspring of consanguineous parents. There was no family history of rheumatologic diseases. On physical examination there was hepatosplenomegaly and lymphadenopathy. Neurodevelopmental status and other examinations were normal except pallor in skin and mucosal membranes. His initial blood count showed a hemoglobin level of 8 g/dl, platelet count of 110,000/ μ l and white blood cell count of 6,300/ μ l. Liver function tests and lipid profiles were normal. PPD test and direct and indirect coombs were negative. The chest x-ray was normal, while an abdominal ultrasound revealed hepatosplenomegaly. In bone marrow aspiration (two times), mild myeloid hyperplasia was reported. Lymph node biopsy showed non-specific reactive hyperplasia. Serologic evaluations of infectious diseases (HIV, EBV, CMV, HCV, HBV, -toxoplasmosis and visceral leishmaniosis) were negative. Autoimmune markers (ANA, Anti ds-DNA and RF) were also negative. Ten months later he was admitted because of massive lymphadenopathies in cervical chains accompanying petechial and purpuric rashes. There was also hepatosplenomegaly. At this time his hemoglobin level was 7.8g/dl and the platelet count was 7,000/ μ l. Serum immunoglobulin evaluation showed elevation in the IgG level (hypergammaglobinemia). Peripheral blood lymphocytes were analyzed by flow cytometry for double negative T cells, using monoclonal antibodies against blood cell markers. The blood sample showed 11% of double negative cells with a normal CD95 marker (Fas). A confirmatory diagnostic test (3-color immunophenotyping of DNT cells, in vitro assay for Fas-mediated apoptosis) of his blood sample was carried out that demonstrated defective in vitro lymphocyte apoptosis. The "Phosphatidyl Serine Detection" kit (IQ Products, Netherland) used to measure apoptosis of isolated T lymphocytes according to manufacturer's instructions. One part of isolated T lymphocytes was washed in calcium buffer and adjusted to 1.5×10^6 cells/ μ l. To the 100 μ l of cells, 10

μ l FITC labeled Annexin V was added and incubated 20 min on ice in the dark. After incubation 2 ml cold calcium buffer was added and cells were washed and centrifuged for 5 min at 1200 rpm. Then for 10 μ l propidium iodide was added and incubated for 10 min on ice and analyzed by BD flow cytometry. By using this kit we differentiated viable cells (Annexin V⁻ PI⁻) from early apoptotic (Annexin V⁺ PI⁻), late apoptotic (Annexin V⁺ PI⁺), and necrotic cells (Annexin V⁻ PI⁺). After diagnosis, he was treated with prednisolone (1 mg/kg/day). Due to a poor response to corticosteroid, azathioprine was started. After 2 months, significant decrease in the size of lymph nodes was seen and platelet count increased.

DISCUSSION

To the best of our knowledge, one case of ALPS was reported in our country to date and this patient may be the second case that indicates the need for more attention to this syndrome during evaluation of patients with reticuloendothelial system manifestations.

The molecular basis of ALPS was identified in 1995 as a Fas-encoding gene mutation. Fas is a receptor expressed on activated lymphocytes that programs cell death.^{8,9} Age of manifestation is 6 months to 18 years old. There were six types of ALPS in the base of causative mutations: type 0 and 1a of ALPS are due to homozygous and heterozygous Fas mutation, type 1b due to defect of the Fas ligand, type 2a due to mutations in the caspase-10 gene, type 2b due to mutations in caspase-8 genes and type 3 due to an unknown genetic defect.¹⁰⁻¹³

Our patient did not have type 0 or 1a of ALPS because CD95 markers were normal, so he belongs to the other types of ALPS. Diagnosis of type requires mutation assessment that was not available in our institution.

ALPS is an uncommon disease which presents with common signs. The clinical manifestations and laboratory data of ALPS raise a broad differential diagnosis such as hematologic malignancies, storage diseases, infections, rosai-dorfman syndrome and others. But it seems that ALPS is under-diagnosed. It is important to know clinical and laboratory findings of this syndrome for appropriate diagnosis, accurate treatment and determination of prognosis.^{6,14}

In conclusion, ALPS should be suspected in all patients with massive lymphadenopathy and

hepatosplenomegaly, especially with evidence of cytopenia and hypergammaglobinemia.

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