

Autoimmune Lymphoproliferative Syndrome; A Case Report

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ABSTRACT

Autoimmune lymphoproliferative syndrome is a disorder of lymphoid system regulation characterized by chronic splenomegaly, lymphadenopathy and autoimmune phenomena especially immune-mediated cytopenias. The hallmark of the disease is the presence in peripheral blood and lymphoid tissue of increased numbers of a normally rare T lymphocyte subset, usually referred to as “double-negative” T cells. Here the authors report a 16-year-old boy when he was first hospitalized for diffuse petechiae, purpura and epistaxis at 9 years of age. One year later, he was readmitted for high fever and recurring cytopenia. On examination several enlarged, nontender lymph nodes involving cervical and submandibular areas and a huge spleen were detected. Lymph node biopsy was performed two times. According to flowcytometry of peripheral blood and immunophenotyping of lymph node tissues which revealed increased numbers of CD3⁺CD4⁻CD8⁻ T-lymphocytes autoimmune lymphoproliferative syndrome was suggested for him. Autoimmune lymphoproliferative syndrome should be considered in differential diagnosis of any patient with unexplained Coomb’s positive cytopenias, hypergammaglobulinemia, generalized lymphadenopathy and splenomegaly. The confirmation of the diagnosis should be based upon genetic analysis and detection of the affected genes involved in *fas* pathway.

Keywords: Autoimmunity; Lymphadenopathy; Pancytopenia; Splenomegaly

INTRODUCTION

Autoimmune lymphoproliferative syndrome (ALPS) is a rare disorder in children characterized by splenomegaly, massive lymphadenopathy, autoimmune phenomena such as thrombocytopenia, neutropenia, hemolytic anemia and accumulation of double-negative (CD3⁺CD4⁻CD8⁻)T cells in the blood.^{1,2} In the majority of patients, ALPS is due to inherited mutations in genes encoding proteins of the *Fas* pathway, which mediates programmed cell death or apoptosis.³ The ALPS phenotype is associated with inherited mutations in the CD95 gene (ALPS Type Ia) or the CD95 ligand gene (ALPS Type Ib).

In ALPS Type II, a more severe clinical phenotype is presumed to be caused by an undefined inherited gene defect in the absence of mutations in the CD95 or CD95 ligand genes.⁴ Heterozygous dominant mutations of *Fas* gene were found in children with the autoimmune lymphoproliferative syndrome, which is also known as the Canale-Smith syndrome. The main clinical features of this disease are splenomegaly, lymphadenopathy, hypergammaglobulinemia, and autoimmunity.⁵ Characteristic laboratory features of ALPS include: Defective lymphocyte apoptosis, the accumulation of double-negative (CD3⁺ CD4⁻ CD8⁻) T lymphocytes, and heterozygous mutations in CD95-CD95 ligand genes.⁴ This report describes a 16-year-old boy which based on clinical and laboratory findings ALPS was suggested for him.

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Autoimmune Lymphoproliferative Syndrome

CASE REPORT

This patient was a 9-year-old boy when he was first hospitalized for diffuse petechiae, purpura and epistaxis of one week's duration. On examination, there were extensive purpuric lesions over the upper neck and extremities and the spleen was palpable 2-3 cm below costal margin. Initial complete blood count showed Coomb's positive hemolytic anemia and severe thrombocytopenia. A bone marrow aspiration was performed which revealed increased megakaryocytic and erythroid series. According to above mentioned findings, Evans syndrome was suggested for the patient and corticosteroids (prednisolone 2mg/Kg/day) plus Intravenous Immunoglobulin was started. After 1 month, in an attempt to taper corticosteroids, thrombocytopenia again developed, so this time Cyclosporin, an immunosuppressive drug was started. One year later, he was readmitted for high fever and recurring cytopenia. On examination several enlarged, nontender lymph nodes involving cervical and submandibular areas and a huge spleen were detected. Chest x-Ray revealed bilateral hilar lymphadenopathy and abdominal ultrasonography showed multiple para-aortic lymph nodes. Severe thrombocytopenia and splenomegaly required splenectomy. Serologic tests for Epstein-Barr virus, Cytomegalovirus and HIV were all negative. Because of persistent lymphadenopathy, lymph node biopsy was performed two times at different intervals, suggestive of "nonspecific follicular hyperplasia", each time. There was no evidence of malignancy. Repeated bone marrow aspirations were not diagnostic.

Flowcytometry of peripheral blood reported increased numbers of CD3⁺CD4⁻CD8⁻ T cells (65%). Repeated flowcytometry confirmed this result. Immunohistochemistry of lymph node tissues also showed the same increased double-negative T cells. ALPS was suggested for the patient and he was planned to receive different immunosuppressive drugs. There was a waxing and waning course in his disease. He expired at the age of 16 years due to recurring cytopenia and overwhelming sepsis.

DISCUSSION

Autoimmune lymphoproliferative syndrome is a recently recognized disease which has been defined

using a combination of clinical, laboratory and molecular findings. ALPS can cause significant morbidity.² In some patients solid or hematologic malignancies, including Hodgkin's and Non-Hodgkin's lymphoma also develop.⁶ Three criteria have been proposed by the National Institute of Health ALPS group for diagnosis of ALPS: 1) Chronic accumulation of nonmalignant lymphoid cells 2) An increase in DNT cells in the blood, and 3) Defective in vitro *Fas*-mediated apoptosis.⁷

In our reported case, all of the above mentioned findings resulted in a broad range of differential diagnosis which included infections, metabolic diseases, hematolymphoid malignancies and other heritable immune disorders such as common variable immune disorders and Wiskott-Aldrich syndrome.³ In this regard; a diagnostic workup for infections such as tuberculosis, toxoplasmosis and infectious mononucleosis was performed. He even received treatment for toxoplasmosis because of hypergammaglobulinemia and a positive titer for toxoplasma gondii (IgG indirect fluorescent antibody), although there was no change in size of lymph nodes and clinical course of the disease. We also performed multiple bone marrow aspirations and bone marrow biopsy to rule out possible involvement of the bone marrow as these patients are predisposed to the development of Hodgkin or Non-Hodgkin's lymphoma.^{1,2} Defective T lymphocyte apoptosis results in expansion of activated T and double-negative T cells (DNT)-cell populations, while defective B cell apoptosis mediates hypergammaglobulinemia and increased survival of antibody producing B cells.^{8,9} In the clinical laboratory, the hallmark of ALPS is the presence in peripheral blood and lymphoid tissue of increased numbers of a normally rare T lymphocyte subset, usually referred to as "double-negative" T (DNT) cells, that lack both the CD4 and CD8 surface molecules.³ In normal persons, less than 2 percent of CD3⁺ T cells are double negative.¹ In our case positive Coomb's test and hypergammaglobulinemia seemed to be the result of the defect in apoptotic pathways as he showed evidence of DNT cells in flowcytometry of peripheral blood and immunophenotyping of lymph node tissues. In the majority of patients, ALPS is due to inherited mutations in genes encoding proteins of the *Fas* pathway, which mediates programmed cell death or apoptosis. Apoptosis limits lifespan of

peripheral B and T lymphocytes and eliminates autoreactive T-cell clones.^{3,4} *Fas* also called Apo-1 or CD95 is a cell surface receptor belonging to the tumor necrosis factor receptor superfamily (TNFRSF6); once triggered by its ligand (*Fas* ligand), *Fas* initiates a cascade of events within the cell that culminates in the death of the cell. *Fas* pathway has a crucial role in lymphocyte homeostasis.^{1,2,4} Heterozygous dominant mutations of *Fas* were found in children with ALPS, which is also known as Canale-Smith syndrome.^{4,5,10} The Canale-Smith syndrome, first described in 1967, is an uncommon cause of lymphadenopathy in children. Patients with this syndrome present within the first two years of life with lymphadenopathy, hepatosplenomegaly, hemolytic anemia and thrombocytopenia.^{5,11} Lymph node biopsy reveals nonspecific paracortical hyperplasia with increased numbers of lymphocytes, plasma cells and histiocytes.^{3,4} In our patient, biopsy of lymph nodes was interpreted as “follicular hyperplasia”, without evidence of conversion to Non-Hodgkin’s Lymphoma. In a report from division of pediatrics, university of Pennsylvania, 4 cases with Canale-Smith syndrome have been described. 2 out of 4 cases were 8-year old boys who presented with lymphadenopathy and splenomegaly, respectively. Autoimmune hemolytic anemia and thrombocytopenia developed at the age of 8 months in one of them and at 10 months of age in the other one.⁸ Immunophenotypic analysis of T cells for 4 of 5 patients with ALPS revealed that all had higher levels of DNT cells.³

The major medical complications in infancy and childhood are autoimmune pancytopenia and infections due to splenectomy or neutropenia, so treatment with corticosteroids and immunosuppressive drugs can reduce the degree of lymphadenopathy and improve the cytopenia.¹⁰ In the oldest report by Canale and Smith most of the patients underwent splenectomy.^{10,11} In our patient splenectomy was performed because of mechanical embarrassment and worsening thrombocytopenia. He expired due to overwhelming sepsis while receiving immunosuppressive drugs.

In closing, it is noteworthy that our patient fulfilled most of the criteria required for the diagnosis of ALPS, even though we could not evaluate in vitro defect of lymphocyte apoptosis or detect the affected gene due to lack of these technologies in our university. It is strongly advised that immuno-

hematology departments should be equipped with such facilities for confirmation of diagnosis and investigational purposes. Finally, ALPS should be considered in differential diagnosis of infants and children presenting with splenomegaly, lymphadenopathy and otherwise unexplained cytopenia. Suspicion should be heightened if cytopenia is immune mediated.³ Greater awareness of ALPS should result in a more directed diagnostic approach and earlier initiation of treatment for this disease.

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Autoimmune Lymphoproliferative Syndrome

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