Autoimmune Lymphoproliferative Syndrome: A Case Report

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Abstract

Autoimmune lymphoproliferative syndrome is an impairment of lymphocyte apoptosis expressed by generalized non-malignant lymphoproliferation, lymphadenopathy and/or splenomegaly. We report the case of a 7-year-old male patient presenting with relapsing generalized lymphadenopathy, splenomegaly, bicytopenia (autoimmune hemolytic anemia and thrombocytopenia), and lymphocytosis. Immunological investigations concluded to defective in vitro tumor necrosis factor receptor superfamily member 6 (Fas)-mediated apoptosis and T cells that express the alpha/beta T-cell receptor and lack of both CD4 and CD8 (so-called α/β-DNT cells), and expansion of an unusual population of α/βCD3⁺CD4⁻CD8⁻ (double-negative T cells>1%). Treatment consisted of corticosteroids, intravenous immunoglobulin, and cyclosporine, with favorable outcome.

Keywords

Autoimmune lymphoproliferative syndrome; lymph node; Cytopenia

Introduction

The autoimmune lymphoproliferative syndrome (ALPS), caused by defective lymphocyte homeostasis, is characterized by: non-malignant lymphoproliferation, lymphadenopathy and/or splenomegaly. We report the case of a 7-year-old male patient presenting with relapsing generalized lymphadenopathy, splenomegaly, bicytopenia (autoimmune hemolytic anemia and thrombocytopenia), and lymphocytosis. Immunological investigations concluded to defective in vitro tumor necrosis factor receptor superfamily member 6 (Fas)-mediated apoptosis and T cells that express the alpha/beta T-cell receptor and lack of both CD4 and CD8 (so-called α/β-DNT cells), and expansion of an unusual population of α/βCD3⁺CD4⁻CD8⁻ (double-negative T cells>1%). Treatment consisted of corticosteroids, intravenous immunoglobulin, and cyclosporine, with favorable outcome.

Clinical Case

A 7-year-old male patient without family medical history was admitted with generalized lymphadenopathy, splenomegaly, and epistaxis. There was no history of cutaneous lesions, articular pain, or specific infectious disease. His parents were not related, and there was no history of rheumatologic disease in the family. Physical examination showed mucocutaneous pallor, multiple bruises on trunk and limbs, cervical axillary and inguinal lymphadenopathy, and splenomegaly. Cell blood count revealed bicytopenia consisting of normochromic normocytic anemia of 6 g/dl with reticulocytosis and low platelets count of 27 000 elements/mm³. ESR reached 120 the 1st hour. Serum electrophoresis revealed polyclonal hypergammaglobulinemia to 27 g/l. Antiglobuline test was positive Ig G type. Serologic tests for specific infection diseases including CMV, EBV, HIV, HCV, HBV, leishmaniasis, TPHA/VDRL, Widal, and Right were negative. Blood and stool cultures were negative. Chest X-ray and echocardiography were normal. Abdominal ultrasound confirmed homogenous spleen enlargement. Marrow aspiration rejected hemophagocytic process and did not show Leishman-Donovan bodies. Histopathological analysis of lymph nodes showed reactive follicular hyperplasia. Tests for rheumatoid factor, anti-nuclear factor, and anti-cardiolipin antibody were positive, while anti-extractable nuclear antigens, anti-DNA, and anti- neutrophil cytoplasmic antibody were negative. Immunoglobulin dosage showed elevated Ig G of 20 g/l (normal range 7-14 g/l). Corticosteroids associated to intravenous immunoglobulin induced transient improvement because the patient relapsed 1...
year, then 2, then 3 years after time of diagnosis with the same clinical features. Immunological investigations concluded to defective in vitro tumor necrosis factor receptor superfamily member 6 (Fas)-mediated apoptosis and elevated T cells that express the alpha/beta T-cell receptor but lack both CD4 and CD8 (so-called α/β-DNT cells). Cell surface expression of Fas (CD95) was low. The diagnosis of autoimmune lymphoproliferative syndrome (ALPS) was retained. An immunosuppressive agent, cyclosporine, was used continuously during 2 years with favorable outcome. Lymphadenopathy disappeared and routine CBC remained normal. The patient remained asymptomatic, and the decline is 14 years.

**Discussion**

ALPS is the first human disease whose etiology has been attributed to a primary defect in apoptosis (Bleesing, 2003). Homeostasis through apoptosis is crucial to remain within the limited containment capacity of the lymphoid compartment to eliminate autoreactive lymphocytes and to prevent malignant transformation. A defective apoptosis of lymphocytes through the Fas pathway occupies a central role in the pathogenesis of ALPS. Oliveira et al proposed a revised set of diagnostic criteria based on a constellation of clinical findings, laboratory abnormalities, and identification of mutations in genes relevant to the tumor necrosis factor receptor superfamily member 6 (Fas) pathway of apoptosis (Oliveira et al 2010). Although mutation screening was not performed in our case, the diagnosis of ALPS can be retained based on the two required criteria including chronic (>6 months) non-malignant, noninfectious lymphadenopathy and splenomegaly, and elevated α/β-DNT cells with elevated lymphocyte counts associated to a primary accessory criterion consistent with defective lymphocyte apoptosis. Furthermore, our patient had fulfilled secondary accessory criteria consisting of autoimmune cytopenias and elevated immunoglobulin G levels. Approximately 25% of individuals with ALPS currently lack a genetic diagnosis (Bleesing, 2003).

In our case, the first clinical manifestation was chronic lymphadenopathy and splenomegaly in an otherwise healthy child, and the age of onset (7 years) of these symptoms is considered to be late as compared to reported data where age of onset was typically about 24 months. Clinical manifestations were more severe at the beginning of the disease, with profound cytopenia, bleeding and bruising. The patient did not respond well to a combination of corticosteroids and intravenous immunoglobulins. Cyclosporine was added several years after diagnosis time. Afterwards, we obtain stabilization. This may go with the paralleling age of expansion of the lymphocyte repertoire in children, which tends to improve in adolescents and adults (Turbyville and Koneti, 2003). This conclusion cannot be retained in our case because of the late onset of disease and a real improvement of cytopenia after starting an immunosuppressive agent combined to steroids.

Our patient presented autoimmune manifestations associated to positive autoantibodies (rheumatoid factor, anti-nuclear factor, and anti-cardiolipin antibody) in the absence of overt autoimmune disease. These conditions are frequent in APLS, and other autoimmune manifestations have been reported including Guillain-Barre syndrome, glomerulonephritis, uveitis, and liver disease as well as multiple autoantibodies (Bleesing, 2003).

Individuals with ALPS have an increased risk for both Hodgkin and non-Hodgkin lymphomas, underscoring the role of Fas as a tumor-suppressor gene. The increased risk is respectively 14-fold and 51-fold for non-Hodgkin and Hodgkin lymphomas (Straus et al., 2001). In our case, the patient did not develop signs related to malignancy and the current decline is 14 years.

In the absence of curative treatment, current management is focused on the control and/or treatment of manifestations of lymphoproliferation and/or autoimmunity, and the treatment of lymphoma. The management of our patient consisted first of a long period of prednisone associated to intravenous immunoglobulin. This first line treatment was not enough, and there were multiple relapsing episodes. High-dose intravenous immune globulin (IVIG) does not appear to be as effective in inducing permanent or long-term remission in ALPS as it is in isolated immune thrombocytopenia. Stabilization was obtained after adding an immunosuppressive agent. Treatment strategies remain mostly targeted at the disease.
manifestations, but more specific therapies directed at the primary pathogenic defects might become possible in the future (Bleesing, 2003).

Conclusions
ALPS is surely an underestimated diagnosis. To our knowledge, this is the first published case from Tunisia and North Africa. ALPS should be considered in case of non-malignant lymphoproliferative syndrome associated to autoimmunity manifestations.

References

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