



The lymphoproliferative auto-immune syndrome: a rare cause of peripheral cytopenia

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ABSTRACT

Autoimmune Lymphoproliferative syndrome is an inherited disorder manifesting with autoimmune cytopenia, lymphadenopathy and splenomegaly. The differential diagnosis includes infections, autoimmune disorders or malignancies. The disease is characterized by accumulation of double negative (CD3+ CD4- CD8-) T cells (DNT) in the peripheral blood. Here we report the case of 19 years-old girl that was diagnosed as autoimmune Lymphoproliferative syndrome with a literature review.

Keywords: lymphoproliferative auto-immune syndrome, cytopenia

INTRODUCTION

Autoimmune lymphoproliferative syndrome (ALPS) is a rare inherited disorder occurring in childhood characterized by splenomegaly, massive lymphadenopathy, immune cytopenia and accumulation of double-negative (CD3+CD4-CD8) T cells in the blood (1,2). Here we report the case of 19 years-old girl that was diagnosed as ALPS with a literature review.

CASE REPORT

The patient was referred to the department of internal medicine in October 2011 at the age of 16 with severe anemia and systemic lupus suspicion. She was the first child of non-consanguineous marriage, her brother died at the age of 9 with a severe thrombocytopenia and her sister aged of 8 was hospitalized many times in pediatric department with hemolytic anemia. At the age of 11, the patient was first admitted to the pediatric department with 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 severe thrombocytopenia. The platelet count was 30000 elts/mm³. A bone marrow aspiration was performed and revealed no abnormalities. Viral serologic studies including CMV, EBV, HSV, Rubella, HBV, HCV, HIV and Toxoplasma were negative. The diagnosis of autoimmune thrombocytopenia was made and the patient was treated with high dose of corticosteroids (prednisolone 1 mg/Kg/day) was started with favorable outcome. Later, she has presented the relapses of thrombocytopenia requiring high dose of corticosteroids each time. In January 2011, a splenectomy was performed because of severe relapsing thrombocytopenia with a normalization of platelets counts. In October 2011, she was hospitalized for icterus and fever. Her blood count revealed a hemoglobin level of 4 g/dl, an hematocrit of 29%, white blood cell count of 30.6D109/l, lymphocyte of 11.3109/l, and platelet count of 3.0D109/l. The reticulocyte count was 1%. The direct Coomb's test was positive to Ig G. The diagnosis of auto immune hemolytic anemia was made and the patient was treated with High-dose of corticosteroids with normalization of hemoglobin level. Virological and bacteriological tests were negative. Nevertheless, immunological tests showed a positive antinuclear antibody with a titer of 1/1280. She was transferred to our department for suspicion of systemic lupus. At her admission, her physical examination was normal and then the diagnosis of systemic lupus was ruled out. To investigate the lymphocytosis a whole body tomography showed multiple mediastinal and retroperitoneal and para-aortic lymph nodes and a bone marrow

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aspiration revealed an infiltrate consisting of transforming lymphocytes of 35 %. Flowcytometry of peripheral blood reported increased numbers of CD4⁻CD8⁻ T cells (%).According to the previous findings, the diagnosis of APLS was retained. In April 2017, the patient experienced a severe hemolytic anemia, hemoglobin failed to increase with systemic steroids leading quickly to her death because of multivisceral organ failure and heart attack.

DISCUSSION

Autoimmune lymphoproliferative syndrome (ALPS), was first described by Canale-Smith in 1967. It is a rare disease observed mainly in childhood (3). The main symptoms of this entity are lymphadenopathy, hepatosplenomegaly, autoimmune disorders and sometimes fatal complications such as Hodgkin's and Non-Hodgkin's lymphoma (4,5). APLS is due to heritable mutation in FAS ligand gene programmed death or apoptosis of lymphocytes (6). Autosomal dominant FAS mutation with variable penetrance and expressivity is identified in the majority of APLS cases (7,8). The lack of Fas Ligand expression on lymphocytes leads to defect in apoptosis and then to chronic nonmalignant lymphoproliferation and the accumulation of double-negative (CD3⁺CD4⁻CD8⁻) T cells in the blood and autoimmune manifestations (1,9,10). Most of the autoimmune disorders associated with ALPS target and damage blood cells. Comparatively to our patient, cytopenias are usually chronic and refractory and most severe in early childhood. ALPS-related autoimmunity sometimes targets other organs, leading to conditions such as uveitis, hepatitis, glomerulonephritis, infiltrative pulmonary lesions, and encephalitis and myelitis (manifesting as aseptic meningitis and even or the connective tissues like systemic lupus erythematosus which make the diagnosis more difficult (11). In the present case, there were not a sufficient data to meet the criteria of systemic lupus. So, we insist on the possibility of positivity of antinuclear antibody without organic damages. In fact, in APLS multiple autoantibodies, frequently those against red blood cells presenting as a positive Coomb direct antiglobulin test, have been demonstrated, even in the absence of overt autoimmune diseases (12). The diagnosis of ALPS is currently based on criateria established by the First International ALPS Workshop in 2009 requiring the presence of chronic lymphadenopathy and/or splenomegaly and elevated circulating TCR $\alpha\beta$ ⁺CD4⁻CD8⁻ DNT cells (13). Characteristic histopathologic findings lymph node are also helpful for diagnosis of ALPS-FAS. These include paracortical expansion with infiltration by polyclonal TCR $\alpha\beta$ ⁺ DNT cells accompanied by follicular hyperplasia and polyclonal plasmacytosis (14). In our patient, the family history of autoimmune cytopenia in childhood and the peripheral nonmalignant lymph proliferation were helpful for the diagnosis. Unfortunately, we were unable to evaluate the defect of lymphocyte apoptosis in vitro or detect the affected gene due to lack of these test in our hospital. The risk of transformation lymphoma should be considered in APLS particularly in patient with mutations abrogating function of the intracellular domain of the FAS protein. In fact, the risk of an ALPS patient developing Hodgkin lymphoma is estimated at 50 times that of the general population, and the risk of NHL is increased 14-fold in them (15). The management of ALPS is usually difficult. The recurrent flares of auto-immune cytopenia need a corticosteroid therapy with intravenous methylprednisolone pulses followed oral prednisone (1-2 mg/kg) as a maintenance therapy that can often be successfully tapered over several weeks. Intravenous immunoglobulin is associated to corticostoids in case of severe AIHA. In situation of refractory, chronic cytopenias, MMF and then rituximab constitute the alternative therapy and finally the practice of splenectomy. Allogeneic hematopoietic stem cell transplantation was also successful in selected ALPS patients with lymphoma or refractory cytopenia (16). Patients require a long-term monitoring with periodic CT and DFG PET scan for screening lymphoma. In our case, the auto immune disorders were serious and rapidly fatal so that were unable to associate other immunosuppressant therapy.

CONCLUSION

ALPS should always be considered in the diagnosis of recurrent and refractory peripheral auto immune cytopenia especially when it is revealed in early age. Our case report was also particular by the delay of lymphoproliferative infiltration declared in adulthood. Through the present case we would like to emphasize on the importance of earlier diagnosis and treatment initiation of this disease.

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