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An Unusual Case of Hepatosplenomegaly with Cytopenia

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Abstract

Autoimmune lymphoproliferative syndrome (ALPS) is a rare, inherited disorder of immune dysregulation secondary to defective lymphocyte apoptosis. This leads to uninhibited proliferation of lymphoid tissue manifesting with lymphadenopathy, hepatosplenomegaly, autoimmune cytopenia, and an increased risk of lymphoid malignancy. We report a two- year- old boy with fever, generalized lymphadenopathy, hepatosplenomegaly, bicytopenia and seizure. He was investigated extensively to rule out infectious, malignant and autoimmune causes and was subsequently found to have elevated "double negative" T lymphocytes with other evidence of autoimmunity and hyperglobulinemia. In the absence of molecular diagnostic testing a diagnosis of probable ALPS was made and corticosteroid was started. Though there was initial good response, steroid could not be tapered, so, he was started on mycophenolate and responded to it. It is believed that with common and wide range of manifestations, ALPS is likely to be under-diagnosed and a greater awareness of the entity among pediatricians is required.

Key Words: ALPS, Cytopenias, Double negative T lymphocyte, Lymphoproliferative disorders.

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Introduction

Autoimmune lymphoproliferative syndrome (ALPS) is a rare inherited disorder of apoptosis manifesting with lymphoproliferation, autoimmunity and an increased risk of lymphomas (1). ALPS is also the first well characterized human disease with primary defect in apoptosis (2). The characteristic laboratory finding in ALPS is elevated "Double negative" T cells (DNT), a T lymphocyte subset that express the α/ß T cell receptor but are negative for both CD4 and CD8 ($CD3^+$ $C4^-$ $CD8^-$) (3). Other associated laboratory abnormalities include elevated levels of interleukin (IL)-10, vitamin B12 and defective in vitro lymphocyte apoptosis (4). Medical literature reveals many syndromes of familial, chronic, nonmalignant lymphoproliferative disorder including such as pseudo mononucleosis, pseudo lymphoma and Canale-Smith syndrome, which may be considered antecedents of ALPS (5-7). The clinical manifestations and laboratory findings of this seemingly rare disease includes a broad number of differential diagnosis such as hematologic malignancies, autoimmune disorders, Hemophagocytic lymphohistiocytosis (HLH), storage diseases, infections, rosai-dorfman disease, castleman's disease etc.(1,4). Misdiagnosis of ALPS is not unknown (8) and in a retrospective analysis of children with Evan's syndrome, 58% were actually found to have ALPS (9).

We report a 2- year- old boy with fever, lymphadenopathy, hepatosplenomegaly, bicytopenia and seizure. We could establish the diagnosis of ALPS even in the absence of molecular diagnostic testing facilities, which would be rarely available in a developing country. The child was treated successfully following the recommended therapeutic guidelines and remains asymptomatic in follow up. We report this case as fellow pediatricians are expected to come across such patients with non-malignant lymphoproliferation with cytopenia where the diagnosis could be reached following a rational diagnostic approach and with the available laboratory support.

Case report

A two- year- old boy, born to non-consanguineous couple, developmentally normal and immunized for age, presented with complaints of fever and progressive abdominal distension for 3 months. He also had non bloody, non mucoid loose stools on and off for 2 months, and one episode of focal seizure with secondary generalization about 15 days back. There was no history of jaundice, bleeding from any site, rash, joint symptoms or repeated blood transfusion. On evaluation, found to have anemia, thrombocytopenia with hepatosplenomegaly. He received blood component therapy and bone marrow examination was within normal limits. He was then referred to higher center for further management.

On presentation to our center, the child had stable vital parameters. There was mild pallor with generalized lymphadenopathy and hepatosplenomegaly. Complete blood count revealed anemia, thrombocytopenia and leucocytosis with differential leucocyte count showing lymphocytosis on several occasions. Infections [Tuberculosis (TB), Kalazar, Chronic viral illness including HIV], malignancy (Juvenile myelomonocytic leukemia, Acute leukemia, lymphoma), Autoimmune disorders with lymphoproliferation were the differentials kept in view of clinical and laboratory findings. Peripheral smear did not reveal any monocytosis or blasts. Bone marrow aspiration and biopsy including cytogenetic analysis for leukemia were also within normal limits. Karyotype was 46, XY, fetal hemoglobin was only 0.5% and BCR–ABL was negative. RK 39 antigen and Mantoux test

were negative and serology [Immunoglobulin G (IgG) & Immunoglobulin (IgM)] for Bartonella henselae was non-reactive. Viral infections eg HIV, Epstein–Barr virus (EBV), Cytomegalovirus (CMV) and Parvovirus B19 infections were ruled out with appropriate investigations. Imaging studies of thorax and abdomen revealed lymphadenopathy in mediastinum and abdomen with no evidence of necrosis, hepatosplenomegaly with normal echotexture and there was no pulmonary parenchymal lesion. MRI brain revealed multifocal areas of chronic intracranial bleed in bilateral cerebral hemisphere and basal ganglia. Repeated Fine-needle aspiration cytology (FNAC) and biopsy from cervical lymph node was suggestive of only reactive hyperplasia. Bacterial culture, fungal culture and Mycobacterial growth indicator tube (MGIT) culture for tuberculosis from lymph node aspirate were also non contributory. In view of persistent non-malignant, non infectious lymphadenopathy, autoimmunity mediated lymphoproliferation secondary to immune dysregulation was considered. Further workup revealed elevated "double negative" ($CD3^+$ $C4^-$ $CD8^-$) T lymphocytes, very high serum IgG with a positive direct Coombs test (DCT) and Antinuclear antibody (ANA). Therefore, a diagnosis of probable-Autoimmune lymphoproliferative syndrome (ALPS) was considered as mutation testing facilities for Fas/ Fas ligand and Caspase 10 or lymphocyte apoptosis study to prove dysregulated FAs-induced lymphocyte apoptosis were not available. The family history was reviewed again for presence of family members with chronic cytopenias or other features of ALPS but could not be identified. The child was started on corticosteroids with Prednisolone 1.5 mg/kg/day and showed very good response; became afebrile with regression of organomegaly, resolution of peripheral lymphadenopathy and improvement in thrombocytopenia next 1 month. But on attempted tapering of steroids, there was worsening thrombocytopenia requiring institution of second line therapy with addition of Mycophenolate moefetil (MMF). On MMF, Prednisolone could be tapered and stopped over next 8 weeks and he remained in remission with no palpable organomegaly or lymphadenopathy, normal leucocyte count with a platelet count above 1 lakh/mm^3.

Discussion

Since being first characterized in the early 1990s, there have been many advances in the understanding of pathophysiology, genetic defect, diagnosis and management of ALPS. Dominantly transmitted germline FAS mutations account for most of the cases of ALPS, followed by somatic mutations in FAS and a minority of patients are found to harbor mutations in FAS ligand or CASPASE 10, while in about one third cases the genotype still remains unknown (4). Defective apoptosis of T lymphocytes results in expansion of activated T and double negative T cells, while, defective B cell apoptosis results in an increased survival of antibody producing B cells leading to hypergammaglobulinemia resulting in autoimmune manifestations (10). Initially being considered a single disease, ALPS now comprises a group of disorders which includes RAS-associated autoimmune leukoproliferative disorder (RALD), CASPASE 8 deficiency Syndrome (CEDS), FAS-associated protein with death domain (FADD) deficiency and Protein kinase C delta (PRKCD) deficiency (11).

ALPS most commonly presents with persistent lymphadenopathy and/or splenomegaly in an otherwise healthy child (12). Other manifestations include hepatomegaly, history of splenectomy, autoimmune hemolytic anemia, immune

thrombocytopenic purpura, neutropenia, liver dysfunction, glomerulonephritis, lung infiltrates and eye lesions (13). Our patient also presented with hepatosplenomegaly, generalised lymphadenopathy, autoimmune (DCT positive) hemolytic anemia and thrombocytopenia. He had a seizure secondary to thrombocytopenia related intra-cerebral bleeding. Cytopenias in ALPS result from autoimmune destruction or splenic sequestration. Some cases are also known to present with eosinophillia and monocytosis (14). Our patient also had monocytosis initially, making Juvenile myelomonocytic leukemia (JMML), a diagnostic possibility. Lymph node histopathology typically involves para-cortical expansion with immunoblasts and DNT cells along with florid follicular hyperplasia (4), which in the absence of immunohistochemistry was reported as only reactive hyperplasia in our patient. ALPS being an inherited disorder, a positive family history for nonmalignant, noninfectious lymphadenopathy and/or splenomegaly ± cytopenias might help suspect the diagnosis (15). But such history was not forthcoming in our case.

The first line treatment for ALPS involves oral corticosteroids i.e. Prednisolone at a dose of 1-2 mg/kg/day for 1 week followed by slow taper over next 8-12 weeks. Intravenous immunoglobulin (IVIG) is advised in cases of severe cytopenias. In cases of no response to above, corticosteroid pulse therapy with IV methylprednisolone is recommended ± IVIG. But if there is breakthrough cytopenias on attempted tapering of Prednisolone, then addition of Mycophenolate moefetil (MMF) is recommended. Patients who don't show good respond to these agents are considered for further immunosuppressive therapy with Sirolimus or Rituximab (4). Our patient also showed initial good response to standard doses of corticosteroids but developed worsening thrombocytopenia requiring addition of MMF. As the lymphadenopathy and splenomegaly often seems to get better with age, if otherwise asymptomatic, most of the patients do not need any intervention for them. Though, use of spleen guard may be considered to prevent catastrophic rupture of spleen. It is advised to avoid splenectomy and to keep vigilance for lymphomas with periodic CT and FDG-PET scans (4). Morbidity and mortality in ALPS depends on the severity of the cytopenias, hypersplenism, and asplenia-related sepsis with the development of lymphoma. The prognosis of ALPS seems to be good with only 13 reported deaths in the largest cohort of 257 patients (4).

Conclusion

Hepatosplenomegaly and cytopenias are not uncommon presentation in pediatric practice. This case reemphasizes the fact that pediatricians should keep the possibility of a rare diagnosis such as ALPS when common causes of such manifestations are ruled out with appropriate investigations and the diagnosis still remains elusive.

Conflict of Interest: None.

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