Autoimmune Lymphoproliferative Syndrome: Response to Mycophenolate Mofetil and Pyrimethamine/Sulfadoxine in a 5-Year-Old Child

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Abstract Autoimmune Lymphoproliferative Syndrome (ALPS) is a rare inherited disorder of disrupted lymphocyte homeostasis characterized by chronic splenomegaly and lymphadenopathy of early onset, hypergammaglobulinemia (Ig G and Ig A), autoimmune phenomena, and expanded populations of TCR- α/β +, CD3+, CD4-, CD8-T cells (Fisher et al. *Cell* 81:935–946; 1995), called double negative T-cells [(DN) T cells]. We discuss a case of ALPS which showed good response to immunosuppressant drug Mycophenolate-Mofetil in combination with Pyrimethamine/Sulfadoxine.

Keywords Autoimmune lymphoproliferative syndrome · Mycophenolate-Mofetil · Pyrimethamine/Sulfadoxine

Introduction

Autoimmune lymphoproliferative syndrome is a chronic non-malignant lymphoproliferative disorder caused by mutations in the genes involved in programmed cell death [2]. It is inherited as an autosomal dominant pattern with variable penetrance. ALPS was first described by Canale and Smith in 1967 and is revealed early in life usually before 5 years of age. The mutation in most ALPS patients are in the gene encoding the lymphocyte protein FAS [3].

FAS are a receptor expressed on activated lymphocyte that mediates programmed cell death. These patients also have autoantibodies most often directed to red blood cells, neutrophils and platelets manifesting as hemolytic anemia, autoimmune neutropenia and immune thrombocytopenic purpura. ALPS patients have lymphocytosis and a number of lymphocyte abnormalities including marked expansion of T lymphocytes that express alpha/beta T cell receptors but no CD4 and CD8 surface markers (TCR α/β + CD4–CD8). Lymphoproliferation in ALPS patients is generally benign, but they are at increased risk for developing Hodgkin's and Non Hodgkin's lymphoma. Definite treatment modalities have not been established so far. Varieties of immunosuppressive drugs have been tried. We successfully treated a patient with Mycophenolate Mofetil and weekly Pyrimethamine/Sulfadoxine (fancidar).

Case Report

A 5-year 3-month-old girl born to a non-consanguineous marriage presented with increasing pallor of one-month duration, fever and right axillary swelling with history of having received two blood transfusions. She was also started on anti tuberculosis drugs prior to coming to our centre. She did not have family history of receiving blood transfusions or similar illness in the family. On examination, she had severe pallor, mild icterus, multiple cervical (2 × 2 cm), axillary (3.5 × 2 × 2 cm) lymphnodes, splenohepatomagaly (6 and 3.5 cm respectively) and protein energy malnutrition grade1. She had no evidence of cutaneous bleed and fundus was normal. On investigation, lab studies revealed anemia (Hemoglobin 3.2 g%, reticulocytes 6.2%, total leucocyte count 3900/cumm, neutrophils 62%, lymphocyte 31%, monocyte 03%, eosinophil

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02%, Platelets = 3,33,000 cumm). Peripheral smear showed marked anisopoikilocytosis and polychromasia. Total Bilirubin 2.2 mg/dl, Direct bilirubin 0.6 mg/dl. Direct Coomb's test was positive (3+). Complement levels, antinuclear antibody and anti double stranded DNA antibody were normal. Bone marrow smear and biopsy revealed megaloblastic change in erythroids with myeloid maturation and adequate megakaryocytes. Lymphnode biopsy showed reactive hyperplasia. There were no abnormal cells in bone marrow or lymph node biopsy. Mantoux test was negative and Chest X-ray was normal. Renal function test was also normal. HIV serology was non reactive and hepatitis B surface antigen & anti hepatitis C serology was negative (Tables 1, 2).

A diagnosis of autoimmune hemolytic anemia was made and she was initiated on Prednisolone (2 mg/kg) with no sustained response for 10 months. Subsequently, she evolved to have Evan's Syndrome suggested by the development of anti platelet antibodies. She continued to have recurrent relapses with partial response to intravenous Immunoglobulins and steroids. In view of persisting lymphadenopathy and splenohepatomegaly and autoimmune cytopenias, Immuno-phenotyping of peripheral blood was sent which revealed Double negative T-cells of 4.88%, (Healthy Control 0.93%), CD3 52.4%, CD4 26.5%, CD8 21.9% and CD20 24.4% suggestive of ALPS.

Table 1 ALPS-features

Non malignant lymphoproliferation
Chronic splenomegaly
Polyadenopathies
Autoimmune manifestations [4, 5]
Hemolytic anemia
Thrombocytopenia
Neutropenia
Other Autoimmune manifestation
Biological features
Hyper-IgG (±Hyper IgA)
High number of double negative (TCR + T Cells in blood and lymphoid tissues)
Autoantibodies
Family history
Lymphoproliferative syndrome
Autoimmune manifestation
Histological features [6]
Reactive follicular hyperplastic and paracortical expansion with immunoblasts and plasma cells.
Splenic tissue from patients demonstrates lymphoid hyperplasia of the white pulp due to B cells expansion in the lymphoid follicles, while T cells accumulates in paracortical areas.

Table 2 Genes associated with ALPS [7]

FAS (TNFR SF6)
ALPS0—Homozygous in FAS
ALPS1—Heterozygous FAS germline mutations, accounts for 75% of individuals with ALPS
ALPS 1A-SM—Somatic mutations in selected cell population, including/β DNT cells in individuals with ALPS with a phenotype similar to that caused by FAS germline mutations
FAS-LG (TNFR SF6)
ALPS 1B—an with germline mutations in FAS LG
CASP-10
ALPS-11—Homozygous and Heterozygous mutations in CASP-10
Other loci
ALPS-111—if all known genetic defects have been ruled out.

As she developed relapses on long term steroids, she was started on mycophenolate mofetil 250 mg (15 mg/kg) BD and Tab Pyrimethamine- sulfadoxine (25/200 mg) weekly for 4 weeks. On this treatment, she has shown very good response and has been transfusion independent for one and a half year.

Discussion

ALPS should be kept as important differential diagnosis in dealing a child with autoimmune hemolytic anemia, Evans syndrome, lymphadenopathy and splenohepatomegaly. So far there are no curative treatment modalities for this entity apart from bone marrow transplantation. Initial line of treatment for most patients is either prednisolone alone or in combination with intravenous Immunoglobulin. Patients with immune cytopenia refractory to splenectomy and steroid treatment can be treated with variety of agents including, cyclosporin A, vincristine methotrexate, azathioprine, mycophenolate [8], rituximab. Mycophenolate mofetil is derived from fungus *Penicillium stoloniferum*. It inhibits inosine mono-phosphate dehydrogenase, the enzyme that control rate of synthesis of guanine mono-phosphate in the denovo pathway of purine synthesis used in the proliferation of B & T lymphocytes. It is more lymphocytic specific and is associated with less bone marrow suppression and fewer opportunistic infections.

Pyrimethamine/sulphadoxine and Mycophenolate separately has been shown to significantly reduce lymphoproliferation and autoimmune cytopenias in a small series of patients with ALPS. In our patient use of mycophenolate and weekly.

Pyrimethamine/sulphadoxine has shown good response. Combination therapy in this patient may be attributing to a better response.

Conclusion

ALPS is a condition to be looked for in a child with autoimmune features. This can be controlled to a certain extent with Mycophenolate Mofetil and Pyrimethamine/sulphadoxine.

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Conflict of Interest None.

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