

## Autoimmune Lymphoproliferative Syndrome (ALPS): A Rare Cause of Immune Cytopenia

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### ABSTRACT

*Autoimmune Lymphoproliferative syndrome (ALPS) 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. We describe a case and review the literature.*

**Key words:** *Autoimmune lymphoproliferative syndrome, Double negative T cells.*

### INTRODUCTION

Autoimmune Lymphoproliferative Syndrome (ALPS) is an inherited lymphoid disorder which results from mutations in molecules involved in the *Fas-Fas* ligand pathway(1). Patients usually present with non malignant enlargement of the lymphoid organs and features of an autoimmune disorder. Mouse models with *Fas* mutation (TNFRSF6 gene) and *FasL* mutations (TNFSF6 gene) cause the *lpr* and *gld* phenotypes characterized by lymphoproliferation, with autoimmune manifestations, and

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*Manuscript received: May 15, 2007;  
Initial review completed: June 5, 2007;  
Revision accepted: August 8, 2007.*

increased T cell receptor  $\alpha/\beta^+$ CD4-CD8- T cells [CD3<sup>+</sup>double negative (DNT)](2). ALPS is the first human disease whose etiology has been attributed to a primary defect in apoptosis or programmed cell death. Awareness of this disease is important as the differential diagnosis includes common autoimmune disorders such as autoimmune hemolytic anemia and immune thrombocytopenia. In a recent retrospective analysis of children with Evan's syndrome, 58% were found to have ALPS(3). There has been no report from India. We report and comment on a case that was diagnosed at our centre.

### CASE REPORT

A six-year old boy, second child of a consanguineous marriage, presented with low grade fever and bleeding gums of two weeks duration. Physical examination was remarkable for pallor, generalized lymphadenopathy and hepatosplenomegaly (5 and 6 cm respectively). Laboratory evaluation showed anemia (Hb: 54g/L), thrombocytopenia (Platelet:  $5 \times 10^9/L$ ), leucopenia with lymphocytosis (WBC:  $2.4 \times 10^9/L$ , lymphocyte 80%) and the direct Coomb's test was positive (3+). The bone marrow trephine biopsy showed solidly cellular marrow with myeloid hyperplasia, increased megakaryocytes and markedly increased reticulin. Autoimmune markers (ANA-neg, dsDNA-WNL, Rheumatoid factor-neg, Complement: 80%) and HIV, HBsAg and HCV were negative and his serum triglycerides and fibrinogen were in the normal range. Serum immunoglobulin levels were normal. Immunophenotyping of peripheral blood revealed increased B cell percentage with kappa restriction (CD2-47%, CD3-49.1%, CD5-51.2%, CD7-41.9%, CD19-38.5%, HLA DR-46.5%, CD20-51.3%, CD38-32.8%, SMIG-50.6%, Kappa-61.1%, Lambda-6.9%). Abdominal ultrasound revealed hepatosplenomegaly. A cervical lymph node biopsy showed nonspecific reactive hyperplasia with preserved architecture displaying follicular hyperplasia and prominent germinal centers.

Peripheral blood lymphocytes were analyzed by flow cytometry for double negative T cells (CD3<sup>+</sup>CD4<sup>-</sup>CD8<sup>-</sup>DNT). Healthy control showed the expected <1% double negative (CD4 and CD8 negative cells) while the patient's sample showed 17.14% of double negative cells.

The patient was diagnosed to have ALPS on the basis of (i) lymphadenopathy with splenomegaly, (ii) non specific lymph node hyperplasia and preserved architecture, (iii) raised circulating double negative T cells and (iv) autoimmune cytopenia. He fulfilled two required criteria and 2 supportive criteria (**Table I**).

Prior to the definitive diagnosis, he was treated with 1 mg/kg/day of prednisolone for 1 month and immunoglobulin 2 g/kg (in 2 days) with no significant hematological response. Following the definitive diagnosis he was treated with weekly doses of trimethoprim-sulphadoxime (25/500 mg) combination for 4 weeks and later with mycophenolate mofetil (250 mg BD×1 month) with no response. After 4

months of supportive therapy, he succumbed to sepsis.

## DISCUSSION

The immune response to infectious agents results in the expansion of antigen-specific lymphocytes, some of which could become harmful to the host. The maintenance of proper homeostasis requires that lymphocyte expansion be appropriately balanced by lymphocyte elimination(1).

ALPS is a chronic, nonmalignant lymphoproliferative disorder caused by mutations in the genes that are involved in apoptosis. This impaired apoptosis leading to accumulation of lymphocytes causes manifestations of lymphadenopathy, autoimmune phenomena and high risk of developing malignant lymphomas. Most of the patients manifest between 6 months to 18 years. The most common autoimmune disorder is immune thrombocytopenic purpura and hemolytic anemia.

There is also accumulation of phenotypically normal CD3<sup>+</sup>CD4<sup>-</sup>CD8<sup>-</sup> T cells (CD3<sup>+</sup>DNT)(4). Autosomal recessive and dominant mutations have been described(5).

ALPS should be suspected in children presenting with autoimmunity and lymphadenopathy. Investigation should include flow cytometric analysis of peripheral blood to look for CD3<sup>+</sup> DNT cells and ideally a test for apoptosis (diagnostic criteria – *Table I*). However, demonstration of defective antigen induced apoptosis in cultured activated lymphocytes *in vitro* requires adequate laboratory support and significant cost.

So far there are no curative treatment modalities for this entity. Initial line of treatment for most patients has been steroids and immunoglobulins with varied responses. Alternative options with pyrimethamine-sulfadoxime (Fansidar<sup>®</sup>) and mycophenolate mofetil have been shown to have the good response rates (100% clinical response in 7 patients and 92% hematological response in 13 patients respectively)(6,7). Other modalities of immunomodulation with vincristine and rituximab have also been tried. Bone marrow transplant has been done successfully in two cases with severe, worsening clinical phenotype(8). Because ALPS has only

**TABLE I** DISEASE DEFINITION AND CLASSIFICATION OF ALPS(1)

### Required feature

- Chronic nonmalignant lymphoproliferation ± splenomegaly
- Raised (>1%) circulating DNT cells
- Defective antigen induced apoptosis in cultured activated lymphocytes *in vitro*

### Supportive features

- Autoimmune disease
- Positive family history of ALPS
- Characteristic lymph node or splenic histology\*
- Mutation in gene coding for Fas

### ALPS classification

- Ia - TNFRSF6 mutation
- Ib - Fas ligand gene mutation
- II - Caspase 8 or 10 gene mutation
- III - Unknown genetic cause

Where identification of *FasL*, *caspase 8* and *caspase 10* mutations is not available, ALPS is more practically classified as type Ia or type non-Ia. \*Architectural preservation, florid reactive follicular hyperplasia and marked paracortical expansion with immunoblasts and plasma cells(9)

recently been identified and classified as a distinct disease, accurate long-term follow-up data does not exist. It is important to accurately diagnose this entity both for appropriate supportive treatment and for accurate prognostication.

#### ACKNOWLEDGMENTS

We thank Dr Mammen Chandy and Dr Alok Srivastava for helpful discussions.

*Contributors:* MJJ was involved in care of the patient and preparation of the draft. VM was responsible for finalization of the draft and will act as guarantor of the paper. RR was involved in laboratory support.

*Funding:* None.

*Competing interests:* None stated.

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