Why should we study rare diseases like ALPS?

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Background:

In 1990, NIH investigators were referred a 3 year old girl with chronic lymphadenopathy, hepatosplenomegaly and autoimmunity for evaluation of possible chronic EBV-associated illness. Extensive studies excluded EBV infection but documented marked expansion in her tissues and blood of normally rare CD4-/CD8- (double-negative) T cells. With additional such patients, it was postulated that the illness; subsequently named Autoimmune Lymphoproliferative Syndrome (ALPS), is the human equivalent to the MRL/lpr and MRL/gld mice which develop a very similar illness. Historically, studies in Fas-deficient MRL/lpr−/− mice develop massive lymphadenopathy, hepatosplenomegaly, autoimmune nephropathy, and expansion of double-negative (DN) T lymphocytes, and have provided insights into the seminal role of TNFRSF6 (Fas) and apoptosis in lymphocyte homeostasis and the pathophysiology of ALPS in humans. Characteristic increases (≥1%) in circulating double negative (CD3+/CD4-/CD8- TCR alpha-beta+) T lymphocytes, and evidence of defective lymphocyte apoptosis in vitro establishes the diagnosis of ALPS.

Approximately 400 ALPS patients have been studied worldwide over the last 18 years. Currently 269 patients with clinical features of ALPS, belonging to 166 families are enrolled in studies at the NIH Clinical Center and 65% of them have a heterozygous mutation in the Fas (TNFRSF6) gene (ALPS Type Ia) while the remainder have either other mutations or are currently undefined in terms of a genetic defect. ALPS remains a model experiment of nature that continues to teach us a great deal about the regulation of lymphocyte survival and the factors that conspire to yield pathological reactions against self-antigens. It results in accumulation of lymphocytes in lymph nodes and spleen leading to childhood onset chronic refractory multilineage cytopenias.

Lymphomas in patients in families with Autoimmune Lymphoproliferative Syndrome (ALPS):

Inherited defects in lymphocyte apoptosis as a risk factor for lymphoma was first reported (Straus et al, Blood, 2001) in a series of 10 patients in 8 families studied among 130 members with Fas mutations in 39 families. We recently updated our database of the ALPS associated lymphoma cohort studied at the NIH Clinical Center. It consists of seventeen patients (12 males and 5 females) from 13 families, including 6 patients previously reported in 2001(2,3). Their median age at lymphoma diagnosis was 17 years (range 6.9 years to 60 years). Nine patients had Hodgkin lymphoma (HL), 8 patients had B cell non-Hodgkin lymphoma (NHL). Fifteen out of 17 patients had germline heterozygous mutations of the Fas gene.
affecting the intracellular portion of the protein, one patient had germline mutation in the NRAS gene and one patient had no mutation detected in the Fas or NRAS genes.

The last two patients, one with Fas mutation and the other with no identifiable genetic mutation were suspected of ALPS only after their lymphoma was diagnosed and/or was in remission with recurrence of reactive lymphadenopathy. This underscores the importance of surveillance for lymphoma and ALPS in families using CT and PET scans with pertinent clinical history (2,3). ALPS should be suspected in patients with a history of previous lymphoma presenting with non-malignant lymphadenopathy during follow up. This series only consists of 17 patients whose lymphoma diagnosis was made in consultations with investigators at NIH.

**Develop strategies to further characterize the underlying pathobiology of antibody driven secondary autoimmune disorders including chronic refractory cytopenias:** Paradigms derived from managing a large cohort of patients with a rare disease like ALPS help us to understand lymphoma biology, streamline care of asplenic patients of diverse etiology, while exploring treatment approaches for more widely prevalent yet refractory immune-mediated hematological cytopenias like chronic ITP (4-8). ALPS is also a valuable model to study the role of spleen in immune dysregulation as nearly 50% of patients being followed long term in our clinic for the last 15+ years have undergone surgical splenectomy as treatment for their refractory cytopenias. Lessons learnt from studying ALPS can lead towards a cogent approach for further work up using current and emerging genomic and proteomic tools aiding management of patients with chronic and refractory cytopenias secondary to an underlying autoimmune and/or infectious etiology.

**Management Suggestions for ALPS Associated Chronic Refractory Cytopenia**

![Diagram of management suggestions for ALPS associated chronic refractory cytopenia]

- **Initial treatment:**
  - Oral prednisone (1-2mg/kg/day) for 2 weeks, then taper slowly over 6 to 8 weeks.
  - IV Ig

- **No Response:**
  - IV methylprednisolone (1-5mg/kg/day) X 3 days + IV Ig (dose based on clinical severity of cytopenia)
  - Followed by oral prednisone (2mg/kg/day) tapered slowly over 8-12 weeks

- **Initial Response with breakthrough cytopenia during corticosteroid tapering**
  - Dose oral prednisone to 1-2mg/kg/day and commence slow taper again over 12 weeks
  - Add oral mycophenolate mofetil (MMF) 1-2g/day divided twice daily

- **Response to MMF with breakthrough cytopenia**
  - Consider short term pulse dose of corticosteroid (oral prednisone 1-2mg/kg/day or higher equivalent dose up to 1mg/kg/day based on clinical severity of cytopenia) and/or continuing MMF

- **Lack of sustained response to MMF**
  - Consider other immunosuppressive and immunomodulatory agents

- **No Response:**
  - Consider Rrituximab

- **No Response:**
  - Assess for splenectomy

- **No Response: Assess for splenectomy**
  - **If hyperplasia is indeed causing cytopenia**
Some Key References:


