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Autoimmune Lymphoproliferative Syndrome: an update and review of the literature

Shaili Shah, MD,
Allergy/Immunology Clinical Fellow, University of North Carolina School of Medicine, Division of Rheumatology, Allergy, and Immunology, Department of Medicine, Chapel Hill, NC 27599, snshah@unch.unc.edu

Eveline Wu, MD, and
Clinical Assistant Professor of Pediatrics, University of North Carolina School of Medicine, Division of Rheumatology, Allergy, Immunology, Department of Pediatrics, CB #7231 Genome Science Building, Chapel Hill, NC 27599, eywu@email.unc.edu

V. Koneti Rao, MD, FRCPA
ALPS Unit, Molecular Development Section, Laboratory of Immunology, DIR, NIAID, National Institutes of Health, DHHS, Room 10/12C106, 10, Center Drive, Bethesda, MD 20892-1899, korao@niaid.nih.gov

Abstract

Autoimmune lymphoproliferative syndrome (ALPS) is characterized by immune dysregulation due to a defect in lymphocyte apoptosis. The clinical manifestations may be noted in multiple family members and include lymphadenopathy, splenomegaly, increased risk of lymphoma and autoimmune disease, which typically involve hematopoietic cell lines manifesting as multilineage cytopenias. Since the disease was first characterized in the early 1990s, there have been many advances in the diagnosis and management of this syndrome. The inherited genetic defect of many ALPS patients has involved (FAS) pathway signaling proteins, but there remain those patients who carry undefined genetic defects. Despite ALPS having historically been considered a primary immune defect presenting in early childhood, adult onset presentation is increasingly becoming recognized, and more so in genetically undefined patients and those with somatic FAS mutations. Thus, future research may identify novel pathways and/or regulatory proteins important in lymphocyte activation and apoptosis.

•Corresponding Author: Teresa K. Tarrant, MD, Assistant Professor of Medicine, University of North Carolina School of Medicine, Division of Rheumatology, Allergy, and Immunology, Department of Medicine, Thurston Arthritis Research Center, Lineberger Cancer Center Member, CB #7280, 3300 Manning Dr., Chapel Hill, NC 27599, tarra002@med.unc.edu.

Compliance with Ethics Guidelines

Conflict of Interest
Shaili Shah, Eveline Wu, V. Koneti Rao, and Teresa K. Tarrant declare no conflict of interest.

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Keywords

Review; Autoimmune lymphoproliferative syndrome (ALPS); Apoptosis; Autoimmunity; Primary immunodeficiency

Introduction

Autoimmune lymphoproliferative syndrome (ALPS) is a disease characterized by immune dysregulation due to an inability to regulate lymphocyte homeostasis through abnormalities in lymphocyte apoptosis or programmed cell death. This defect leads to a lymphoproliferative disease with clinical manifestations that can include lymphadenopathy, hepatomegaly, splenomegaly, increased risk of lymphoma, and autoimmune diseases (typically involving hematopoietic cell lines). The signature laboratory abnormalities in ALPS include an expansion of T cells that express the alpha/beta T cell receptor but lack both CD4 and CD8 in peripheral blood and tissue samples (double negative T cells, DNTs). Other characteristic laboratory findings include elevated levels of interleukin-10, vitamin B12, and defective Fas-mediated apoptosis *in vitro*. In two-thirds of the cases, the genetic defect in the *FAS* gene has been established; however, in many cases, it remains undefined.

Epidemiology and Pathogenesis

There have been nearly 500 patients originating from more than 300 families identified with ALPS[1]; however, the true incidence and prevalence remains unknown, as many patients remain undiagnosed or misdiagnosed. The disease has been reported in various racial and ethnic backgrounds, and some reports have suggested a male preponderance.

The pathogenesis of ALPS in the majority of patients results from defective apoptosis of lymphocytes mediated through the Fas/Fas ligand (FasL) pathway[2]. Thus, a defect in this pathway leads to expansion of lymphocytes, including self antigen-specific populations, and subsequent autoimmunity. Fas is also thought to play a role in suppression of malignant transformation of lymphocytes, and indeed, ALPS patients carry an increased risk of lymphoma[3]. The pathogenesis remains an ongoing topic of research.

Approximately two thirds of ALPS patients have an identified genetic defect in the *FAS* (Table 1). A germline mutation in *FAS* is the most commonly identified genotype at this time[2]. Others may acquire a somatic mutation in FAS limited to the DNT cells [4]. Other proteins involved in the Fas mediated apoptosis pathway have also been implicated in some patients, including defects in the genes encoding Fas ligand (*FASL*)[5] and caspase 10[6, 7]. A large number of patients who meet the diagnostic criteria for ALPS have undefined genotypes.

The recent awareness of delayed presentations of the disease has led to an increased diagnosis in older patients who might have otherwise been given an alternative diagnosis[8–10]. Many of these patients have had a more indolent course and may have developed their initial symptoms during childhood with either diagnosis delayed due to unusual clinical manifestations, late referral to a tertiary center, or late onset disease due to somatic

mutations in Fas. Additionally, there have been at least seven individuals identified who carried the germline FAS mutation (inherited heterozygotes), were initially asymptomatic, and at some point they were thought to have had a somatic genetic event in the second allele encoding FAS, leading to the clinical symptoms[11].

Clinical Manifestations

The earliest and most common clinical manifestation of ALPS is chronic lymphadenopathy and/or splenomegaly, which have been asymptomatic and incidentally identified during routine physical examinations. ALPS patients can also have multilineage cytopenias that are chronic and can be refractory to therapy. This has generally been thought to be most severe in early childhood, as this is the age at which there is expansion of the lymphocyte repertoire, albeit adults have presented with this as well. ALPS patients may present initially with episodes of fatigue, pallor, and icterus due to hemolytic anemia. They may also develop easy bruising and mucocutaneous bleeding due to thrombocytopenia. Bacterial infections can occur due to neutropenia. There is also potential for developing multiple autoimmune problems of other organs including liver, kidneys, and eyes or of lymphoproliferative disorders involving many different organ systems [12], which may be confused with atypical presentations of systemic lupus erythematosus since anti-nuclear-antibodies (ANA) are not uncommon.

The most common laboratory abnormalities found are cytopenias due to autoimmune destruction or splenic sequestration. Conversely, eosinophilia and monocytosis may also be associated findings[13]. Autoantibodies may be present and include positive Coomb's direct antiglobulin test, rheumatoid factor (RF), or anti-nuclear antigen (ANA). Hypergammaglobulinemia is also frequently present[12]. Serum IL-10, soluble FAS ligand, and vitamin B12 are commonly elevated in ALPS patients with *FAS* mutations and can be useful biomarkers[14, 15] for these patients, but may not be abnormal in those with unidentified genetic mutations. Although not commercially available, flow cytometry of the blood for increased number of DNTs can be performed and is pathognomonic of ALPS.

Diagnosis and Differential Diagnosis

In 2009, an international consensus conference was held, and a revised set of diagnostic criteria was published in 2010 (Table 2) [16]. Based on this set of criteria, *definitive* diagnosis is based on the presence of two required criteria and one *primary* accessory criterion. A *probable* diagnosis is based on the presence of both required criteria plus one *secondary* accessory criterion.

Revised criteria eliminate the lymphocyte apoptosis assay as a required criterion, as it has been found to be a resource intensive assay to perform and may only be available at select centers. Methodology of this assay also varies across centers, leading to variable results. The revised criteria also take into account genetic information and other biomarkers which have been shown to be supportive of a diagnosis of ALPS[14]. These secondary accessory criteria provide additional features that may help to support a diagnosis, even when both primary criteria may not be met. Overall, this revision of the diagnostic criteria facilitates the diagnosis of ALPS, particularly in patients who may present at an older age or in an atypical

fashion due to somatic or successive and cumulative mutations. Increasingly recognized are later presentations of ALPS, in part due to the revised set of diagnostic criteria. A case report was published in 2011 which described a 50 year old man who presented with the clinical syndrome of cytopenias, lymphadenopathy, was found to have elevated DNTs, and diagnosed with probable ALPS[17].

ALPS should be considered as a differential diagnosis due to variable phenotypes that overlap with other syndromes, such as Evans' syndrome, hemophagocytic lymphohistiocytosis (HLH), Castleman's disease, and other lymphoproliferative disorders[10]. Diligent review of family history in both children and adults is helpful in making the diagnosis of a rare inherited genetic disorder like ALPS.

Treatment

Overall, the management of ALPS focuses on treatment of the primary disease manifestations and complications since a cure for the genetic defect is presently not possible. The bulk of management focuses on treating disease specific complications, including lymphoproliferation and autoimmune cytopenias with immunosuppression.

The initial therapy for autoimmune multilineage cytopenias is similar to that of other immune mediated chronic and persistent cytopenias. Initial therapy involves high dose corticosteroids +/− intravenous immune globulin (IVIG). High-dose pulse therapy with intravenous (IV) methylprednisolone (starting at 5–10 mg/kg, though doses up to 30 mg/kg have been used), followed by low dose oral prednisone (1–2 mg/kg) maintenance therapy has been successful in many patients. IVIG is generally given concomitantly with pulse dose methylprednisolone at doses of 1–2g/kg [1]. Other steroid sparing agents that have been trialed in ALPS include rituximab[18, 19], mycophenolate mofetil (MMF)[20], and mammalian target of rapamycin (mTor) inhibitors such as sirolimus[21, 22]. Pentostatin has also been used with success in some children with refractory cytopenias[23].

The use of MMF was first described in 2005 by Rao et al. MMF is a prodrug of mycophenolic acid, which is a reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH) in purine (guanine) biosynthesis that is ultimately necessary for the growth of both T and B cells. Thus, suppressing T and B cells limits autoimmune destruction of healthy cells. MMF has been used in various autoimmune disorders, including psoriasis, systemic lupus as well as autoimmune cytopenias[24]. With regards to ALPS, MMF has been used successfully as a steroid-sparing agent in more than 50 cases, and is most commonly used to treat autoimmune manifestations such as cytopenias [20, 25]. MMF is usually given concomitantly with high dose IV corticosteroids initially, and then continued while tapering oral prednisone, with an overlap of at least 2 weeks in order to allow MMF to achieve therapeutic levels. MMF has also been used for other autoimmune complications of ALPS, including uveitis, glomerulonephritis, hepatitis and autoimmune infiltrative pulmonary disease.

Sirolimus has also been used successfully to treat refractory cytopenias, as well as other autoimmune manifestations of ALPS in those failing initial corticosteroids and IVIG. In 2009, Teachey et. al described four patients treated for autoimmune cytopenias, all with

excellent response, as well as two patients treated for autoimmune arthritis and colitis who demonstrated marked improvement in their clinical severity. In addition, three of these patients had resolution of adenopathy and splenomegaly, and all had a reduction in their DNTs[21]. Thus, mTor inhibitors may be a good option for patients who fail corticosteroids, MMF, and present with massive adenopathy and splenomegaly leading to cytopenias.

Pentostatin has been used by some to treat patients with refractory cytopenias. Bajwa et. al. [23] described a case of ALPS presenting at birth that was refractory to splenectomy and immunosuppressive therapy, but responded to pentostatin followed by hematopoietic stem cell transplantation.

Rituximab has been used in many autoimmune diseases, including autoimmune hemolytic anemia and idiopathic thrombocytopenic purpura[26]. There has been controversy regarding its use in ALPS, as it has been noted to cause a permanent hypogammaglobulinemia requiring replacement therapy in some patients and unsustained benefits in others. Rao et. al. [18] described the use of rituximab in twelve ALPS patients. In seven out of nine patients with ALPS and autoimmune thrombocytopenia, rituximab led to a median response duration of 21 months. However, none of the 3 children treated with rituximab for autoimmune hemolytic anemia (AIHA) responded. Toxicities included profound and prolonged hypogammaglobulinemia in three patients requiring IVIG, total absence of antibody response to polysaccharide vaccines lasting up to 4 years after rituximab infusions in one patient, and prolonged neutropenia in one patient. Thus, given risks of additional immunosuppression, rituximab is reserved for cases in which alternative immunosuppressants have failed, and in whom thrombocytopenia seems to be a predominant factor.

Many ALPS patients have been treated with splenectomy in the past to manage chronic, refractory cytopenias, but this is currently not advised[1, 27]. Unfortunately, many patients have had relapse of their cytopenias after splenectomy. However, even more concerning, is that some have had fatal infections, including pneumococcal sepsis. In patients who have had splenectomy prior to their diagnosis, it is recommended that they remain on long-term antibiotic prophylaxis and maintain their vaccinations. In known ALPS cases, splenectomy should only be reserved for patients who have failed all other medical therapies and continue to have life threatening cytopenias that are felt to be due to splenic sequestration. It is imperative to note that more than 50% of the ALPS patients have had their cytopenias relapse after splenectomy proving it to be a futile exercise that only increases their risk of pneumococcal sepsis[27]. Partial splenectomy or splenic embolization should also be considered in these patients as an alternative to complete splenectomy[28].

Other treatments may be on the horizon as we learn more about the molecular mechanisms underlying the clinical manifestations in ALPS. For example, *in vitro*, IL-17 has been found to inhibit Fas-induced cell death[29]. IL-17 neutralization seems to improve lymphocyte apoptosis with ALPS. Treatment with anti-IL-17A antibodies has been shown to ameliorate the autoimmune manifestations and the lymphoproliferative phenotype and prolongs survival in a mouse model of ALPS.

The only curative therapy for ALPS at this time is hematopoietic stem cell transplantation (HCT). Indications for transplant include lymphoma, severe and recalcitrant autoimmune cytopenias, and patients with severe disease phenotype (generally those with homozygous and compound heterozygous FAS defects)[30–32]. However, experience with stem cell transplantation in ALPS is extremely limited with only a few published case reports, and long-term outcomes are yet to be determined. As expected, some cases have been complicated by post-transplant infections as well as graft versus host disease. In one case, a 14-year-old boy with ALPS, lymphoma, and subsequent histiocytic sarcoma underwent a mismatched unrelated donor transplant, complicated by GVHD, methicillin-resistant Staphylococcus aureus pneumonia, and pulmonary hemorrhage, and ultimately he died after three months owing to these complications[33].

In addition to autoimmune disease, ALPS patients have a well-established risk for lymphoma. In cohort of 150 ALPS-FAS patients, 18 patients developed lymphoma and 1 patient another hematopoietic malignancy. When compared to the general population, these patients have a highly significant observed to expected ratio of hematopoietic malignancy [28].

Although there is a risk of lymphoma and life-threatening cytopenias [28], many patients with ALPS, and particularly those with FAS mutations, have their lymphadenopathy decrease over time, and autoimmune complications remain manageable with limited steroid sparing immunosuppression using mycophenolate mofetil and sirolimus. Estimated survival for ALPS-FAS has been reported to be near 85% by age 50, compared to healthy non-ALPS individuals who have an expected survival of 93–95% by age 50. Since many of the recently diagnosed ALPS patients are still children or adolescents, they will need to be studied long-term to determine a more accurate prognosis, risk of lymphoma, and life expectancy.

Conclusions

Autoimmune lymphoproliferative syndrome is a complex disease that now includes patients that may not have been previously recognized. We have learned that onset can be in adulthood and without family history due to somatic mutations, or accumulation of multiple mutations. Many options for management of refractory autoimmune complications have been described, and there is continued research being conducted regarding outcomes in these patients. Further study of ALPS patients and the discovery of previously undefined genetic defects may provide additional insight into immune cell regulation via apoptotic pathways and its role in health and disease.

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References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. Rao VK, Oliveira JB. How I treat autoimmune lymphoproliferative syndrome. Blood. 2011; 118(22):5741–5751. [PubMed: 21885601] Discusses management of various complications related to ALPS based on study of a large cohort of ALPS patients.
2. Fisher GH, et al. Dominant interfering Fas gene mutations impair apoptosis in a human autoimmune lymphoproliferative syndrome. Cell. 1995; 81(6):935–946. [PubMed: 7540117]
3. Straus SE, et al. The development of lymphomas in families with autoimmune lymphoproliferative syndrome with germline Fas mutations and defective lymphocyte apoptosis. Blood. 2001; 98(1): 194–200. [PubMed: 11418480]
4. Hauck F, et al. Somatic loss of heterozygosity, but not haploinsufficiency alone, leads to full-blown autoimmune lymphoproliferative syndrome in 1 of 12 family members with FAS start codon mutation. Clin Immunol. 2013; 147(1):61–68. [PubMed: 23524443]
5. Del-Rey M, et al. A homozygous Fas ligand gene mutation in a patient causes a new type of autoimmune lymphoproliferative syndrome. Blood. 2006; 108(4):1306–1312. [PubMed: 16627752]
6. Zhu S, et al. Genetic alterations in caspase-10 may be causative or protective in autoimmune lymphoproliferative syndrome. Hum Genet. 2006; 119(3):284–294. [PubMed: 16446975]
7. Wang J, et al. Inherited human Caspase 10 mutations underlie defective lymphocyte and dendritic cell apoptosis in autoimmune lymphoproliferative syndrome type II. Cell. 1999; 98(1):47–58. [PubMed: 10412980]
8. Lambotte O, et al. Diagnosis of autoimmune lymphoproliferative syndrome caused by FAS deficiency in adults. Haematologica. 2013; 98(3):389–392. [PubMed: 22983577]
9. Deutsch M, Tsopanou E, Dourakis SP. The autoimmune lymphoproliferative syndrome (Canale-Smith) in adulthood. Clin Rheumatol. 2004; 23(1):43–44. [PubMed: 14749982]
10. Rudman Spergel A, et al. Autoimmune lymphoproliferative syndrome misdiagnosed as hemophagocytic lymphohistiocytosis. Pediatrics. 2013; 132(5):e1440–e1444. [PubMed: 24101757]
11. Magerus-Chatinet A, et al. Onset of autoimmune lymphoproliferative syndrome (ALPS) in humans as a consequence of genetic defect accumulation. J Clin Invest. 2011; 121(1):106–112. [PubMed: 21183795]
12. Neven B, et al. A survey of 90 patients with autoimmune lymphoproliferative syndrome related to TNFRSF6 mutation. Blood. 2011; 118(18):4798–4807. [PubMed: 21885602]
13. Kim YJ, et al. Eosinophilia is associated with a higher mortality rate among patients with autoimmune lymphoproliferative syndrome. Am J Hematol. 2007; 82(7):615–624. [PubMed: 17266055]
14. Caminha I, et al. Using biomarkers to predict the presence of FAS mutations in patients with features of the autoimmune lymphoproliferative syndrome. J Allergy Clin Immunol. 2010; 125(4): 946–@@949.e6. [PubMed: 20227752]
15. Bowen RA, et al. Elevated vitamin B(1)(2) levels in autoimmune lymphoproliferative syndrome attributable to elevated haptocorrin in lymphocytes. Clin Biochem. 2012; 45(6):490–492. [PubMed: 22306884]
16. Oliveira JB, et al. Revised diagnostic criteria and classification for the autoimmune lymphoproliferative syndrome (ALPS): report from the 2009 NIH International Workshop. Blood. 2010; 116(14):e35–e40. [PubMed: 20538792] Discusses current diagnostic criteria for ALPS.
17. Desai NK, et al. Autoimmune lymphoproliferative disorder in an adult patient. J Postgrad Med. 2011; 57(2):131–133. [PubMed: 21654137]
18. Rao VK, et al. Use of rituximab for refractory cytopenias associated with autoimmune lymphoproliferative syndrome (ALPS). Pediatr Blood Cancer. 2009; 52(7):847–852. [PubMed: 19214977]
19. Wei A, Cowie T. Rituximab responsive immune thrombocytopenic purpura in an adult with underlying autoimmune lymphoproliferative syndrome due to a splice-site mutation (IVS7+2 T>C) affecting the Fas gene. Eur J Haematol. 2007; 79(4):363–366. [PubMed: 17725802]

20. Arora S, et al. Autoimmune lymphoproliferative syndrome: response to mycophenolate mofetil and pyrimethamine/sulfadoxine in a 5-year-old child. Indian J Hematol Blood Transfus. 2011; 27(2): 101–103. [PubMed: 22654301]
21. Teachey DT, et al. Treatment with sirolimus results in complete responses in patients with autoimmune lymphoproliferative syndrome. Br J Haematol. 2009; 145(1):101–106. [PubMed: 19208097]
22. Teachey DT, et al. Rapamycin improves lymphoproliferative disease in murine autoimmune lymphoproliferative syndrome (ALPS). Blood. 2006; 108(6):1965–1971. [PubMed: 16757690]
23. Bajwa R, Savelli S, Gross T. Pentostatin for treatment of refractory autoimmune lymphoproliferative syndrome. Pediatr Blood Cancer. 2011; 57(2):336–337. [PubMed: 21495163]
24. Kotb R, et al. Efficacy of mycophenolate mofetil in adult refractory autoimmune cytopenias: a single center preliminary study. Eur J Haematol. 2005; 75(1):60–64. [PubMed: 15946312]
25. Farruggia P, et al. Effectiveness of cyclosporine and mycophenolate mofetil in a child with refractory evans syndrome. Pediatr Rep. 2011; 3(2):e15. [PubMed: 21772952]
26. Liang Y, et al. Rituximab for children with immune thrombocytopenia: a systematic review. PLoS One. 2012; 7(5):e36698. [PubMed: 22666325]
27. Price S, et al. Natural history of autoimmune lymphoproliferative syndrome associated with FAS gene mutations. Blood. 2014; 123(13):1989–1999. [PubMed: 24398331] Discusses long term follow up, including morbidity and mortality, of a large cohort of ALPS patients.
28. Price S, et al. Natural history of autoimmune lymphoproliferative syndrome associated with FAS gene mutations. Blood. 2014
29. Boggio E, et al. IL-17 protects T cells from apoptosis and contributes to development of ALPS-like phenotypes. Blood. 2013
30. Benkerrou M, et al. Correction of Fas (CD95) deficiency by haploidentical bone marrow transplantation. Eur J Immunol. 1997; 27(8):2043–2047. [PubMed: 9295043]
31. Dimopoulou MN, et al. Successful treatment of autoimmune lymphoproliferative syndrome and refractory autoimmune thrombocytopenic purpura with a reduced intensity conditioning stem cell transplantation followed by donor lymphocyte infusion. Bone Marrow Transplant. 2007; 40(6): 605–606. [PubMed: 17618315]
32. Sleight BJ, et al. Correction of autoimmune lymphoproliferative syndrome by bone marrow transplantation. Bone Marrow Transplant. 1998; 22(4):375–380. [PubMed: 9722073]
33. Venkataraman G, et al. Development of disseminated histiocytic sarcoma in a patient with autoimmune lymphoproliferative syndrome and associated Rosai-Dorfman disease. Am J Surg Pathol. 2010; 34(4):589–594. [PubMed: 20216376]

Table 1

Genetic defects most commonly identified in ALPS patients

Gene defect	%
Fas, germline	72%
Fas, somatic	0.5%
Fas ligand	<1%
Caspase 10	<1%
Undefined	20%

Table 2

Current clinical criteria for the diagnosis of ALPS

2010 criteria
Required criteria
Chronic (> 6 months), nonmalignant, noninfectious lymphadenopathy or splenomegaly or both
Elevated CD3+TCRαβ+CD4−CD8− DNT cells (≥ 1.5% of total lymphocytes or 2.5% of CD3+ lymphocytes) with normal or elevated lymphocyte counts
Accessory: Primary
Defective lymphocyte apoptosis (2 separate assays)
Somatic or germline mutation in FAS, FASLG, or CASP10
Accessory: Secondary
Elevated plasma sFASL levels (>200 pg/mL) OR elevated plasma interleukin-10 levels (>20 pg/mL) OR elevated serum or plasma vitamin B12 levels (> 1500 ng/L) OR elevated plasma interleukin-18 levels > 500 pg/mL
Typical immunohistological findings as reviewed by an experienced hematopathologist
Autoimmune cytopenias (hemolytic anemia, thrombocytopenia, or neutropenia) AND elevated immunoglobulin G levels (polyclonal hypergammaglobulinemia)
Family history of a nonmalignant/noninfectious lymphoproliferation with or without autoimmunity

FASLG – FAS ligand gene; CASP10 – Caspase-10 gene; sFASL – soluble FAS ligand