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The expanding spectrum of the Autoimmune Lymphoproliferative Syndromes

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Abstract

1. Purpose of review—Several autoimmune lymphoproliferative syndromes have been described lately. We review here the main clinical and laboratory findings of these new disorders.

2. Recent findings—The prototypical autoimmune lymphoproliferative syndrome (ALPS) has had its diagnostic criteria modified; somatic mutations in RAS genes were found to cause an ALPS-like syndrome in humans; and mutations in a gene encoding a protein kinase C (PRKCD) were discovered to cause a syndrome of lymphoproliferation, autoimmunity and NK cell defect.

3. Summary—The recent discoveries shed light into the molecular pathways governing lymphocyte death, proliferation and immune tolerance in humans.

Keywords

autoimmune lymphoproliferative syndrome; apoptosis; genetics; RAS; PRKCD

INTRODUCTION

Apoptosis is crucial for immune system homeostasis, as lymphocytes undergo massive expansion during encounter with a pathogen and subsequently contract, leaving behind just a few memory cells [1]. It also helps maintain immunologic tolerance, as most self-reactive T and B cells undergo apoptosis during selection in the thymus or bone marrow, respectively [1]. The importance of these mechanisms is illustrated by the clinical findings of humans with genetic defects affecting different apoptotic pathways, here collectively called autoimmune lymphoproliferative syndromes. Although initially composed of one single disorder, the autoimmune lymphoproliferative syndrome (ALPS), caused by defects in genes of the FAS pathway of apoptosis (*FAS*, *FASLG* and *CASP10*), the group has significantly expanded recently, and now includes: RAS-associated Autoimmune Leukoproliferative Disorder (RALD), caused by somatic mutations in *NRAS* or *KRAS*; Caspase-Eight Deficiency Syndrome (CEDS); FADD deficiency; and PRKCD deficiency, the most recently described defect. Each disorder has its own clinical and laboratory particularities, which will be reviewed in this chapter.

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Conflics of interest

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Autoimmune Lymphoproliferative Syndrome

The clinical hallmarks of ALPS are chronic nonmalignant lymphadenopathy, splenomegaly, and multilineage cytopenias [2,3]. The diagnostic criteria for ALPS were revised in 2010 and are presented in Table 1. ALPS usually presents in early childhood, with a median age of onset of 3 years, although a minority of the patients manifest disease later in life, from 18 to 35 years of age [5]. The initial presentation of ALPS is often that of persistent lymphadenopathy and/or splenomegaly (69% of the patients) in an otherwise healthy child [5]. About a quarter of the patients present with an autoimmune disease, most often immune thrombocytopenic purpura (ITP) or hemolytic anemia, in addition to the lymphoproliferation. More rarely, patients present with pure autoimmunity or lymphoma as the initial manifestation of ALPS [5]. Recurrent infections are not a common finding, but can also occur due to neutropenia and/or blockage of nasopharyngeal passages due to lymphadenopathy. Recurrent fevers in the absence of infections are not seen in ALPS.

Regardless of the opening symptoms, lymphadenopathy and/or splenomegaly will eventually be seen in 100% of the patients with ALPS, and are required for its diagnosis [4,5]. Hepatomegaly is found in about half the cases. Areas most commonly affected by lymphadenopathy are the neck, mediastinum, axillae, inguinal and pelvic regions, although virtually any lymph node in the body can be enlarged. The lymphoproliferation tends to improve over time, and after the age of 20 years as much as 66% of the patients will have had complete remission of these manifestations, and the remaining patients will have seen significant improvement [5].

Up to 72% of the patients develop autoimmune manifestations by the age of 30. Most present autoimmune cytopenias (52%), at a median age of 5 years [5]. Autoimmune hemolytic anaemia is the most frequent event, followed by autoimmune thrombocytopenia. Some patients (20%) also develop autoimmune diseases affecting other organs, such as autoimmune hepatitis, glomerulonephritis, uveitis, encephalomyelitis (Guillain-Barre syndrome), aplastic anemia, vasculitis, pancreatitis, angioedema and alopecia [5]. There may also be a family history of similar disorders, usually inherited in an autosomal dominant fashion with incomplete penetrance. Unlike the lymphoproliferation, however, the autoimmune disorders tend to persist in over 60% of the patients, mostly requiring continuous or intermittent immunosuppressive therapy [5].

Laboratory Findings

The defining laboratory finding in ALPS is the presence of an expanded population of $CD3^{+}TCR\text{-}\alpha\beta^{+}CD4^{-}CD8^{-}$ lymphocytes, referred to as the double negative T (DNT) cells [6,7]. These are polyclonal, mature T cells, seen in the peripheral blood and secondary lymphoid tissue of ALPS patients [6,7]. A complete blood count (CBC) with differential may demonstrate lymphocytosis, reticulocytosis, thrombocytopenia, neutropenia, slight monocytosis, and/or eosinophilia.

Other common but less specific findings include polyclonal elevation of IgG and IgA, and the presence of autoantibodies directed to blood cell elements [8]. The most common autoantibodies occurring in ALPS patients are anti-erythrocyte antibodies detected by a

Coombs direct antiglobulin test (DAT), and anti-platelet and anti-neutrophil antibodies [8,9]. Other abnormal laboratory findings that are commonly found in patients with ALPS include elevated serum levels of vitamin B12, IL-10, soluble FAS ligand, and IL-18 [10,11]. The combination of these markers proved to be a powerful predictor of the presence of *FAS* mutations in patients with an ALPS clinical phenotype [10]. Patients with a combination of high DNTs and IL10, Vitamin B12 or have a 97% chance of harboring a *FAS* mutation [10]. These markers were also very sensitive in detecting patients with somatic *FAS* mutations [12]. Thus, in the presence of elevated DNTs and vit. B12 or sFASL, a negative genetic screening for germline *FAS* mutations should prompt an investigation for somatic mutations in the sorted DNT population. These biomarkers were incorporated into the recently modified ALPS diagnostic criteria [4].

A lymph node biopsy can be very helpful to rule out other diagnosis, such as malignancy, and to diagnose ALPS. Findings typical of ALPS include follicular hyperplasia, often with focal progressive transformation of germinal centers, paracortical expansion with a mixed infiltrate containing DNT cells, and polyclonal plasmocytosis [13]. Additionally, up to 41% of the patients with FAS mutations may demonstrate hystiocitic proliferation, resembling sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) [14].

In patients with clinical and/or laboratory features consistent with a diagnosis of ALPS, molecular genetic testing of *FAS* (*TNFRSF6*), Fas Ligand (*TNFSF6*), and caspase-10 genes (*CASP10*) should be obtained. Based on their frequency, we recommend first testing for germline *FAS* mutations, followed by analysis of somatic *FAS* mutations in sorted DNT cells (specially if biomarkers are high). If both tests are negative, *CASP10* and *FASL* should be tested, in any order. The location of specific gene mutation has been shown to be important in patient prognosis as certain mutation loci are associated with a higher risk of complications including lymphoma, and with a higher penetrance [15,16].

Genetics and Pathophysiology

ALPS can be caused by germline or somatic *FAS* mutations and by mutations in *CASP10* and *FASLG*, as discussed below.

Germline FAS mutations—Most ALPS patients (62%) have germline mutations in *TNFRSF6* (*FAS*) [17]. Mutations occur throughout the gene, either in coding regions or in splice sites, with the majority (~2/3) affecting the intracellular death domain (DD) region encoded by exon 9 (Figure 1) [5,16]. Most mutations are heterozygous, transmitted in an autosomal dominant fashion and exert a dominant-negative effect in the FAS pathway [19, 20]. A few ALPS cases with aggressive disease phenotype in early childhood caused by homozygous germline mutations in *FAS* have also been reported [21].

In contrast with the mutations located the intracellular death domain, mutations affecting the extracellular regions of the protein (about 25% of the total) commonly result in loss of protein expression from one allele leading to FAS haploinsufficiency, without a dominant negative effect [16]. These usually manifest by milder clinical disease and lower penetrance [16,22]. More recently, it has been described that up to 60% of ALPS patients with extracellular domain mutations that develop clinically important autoimmune disease

present somatic mutations in the second allele of FAS [5,23,24]. These “second hits” developed later in life and either affected the death domain or caused loss of the healthy allele. This association of germline and somatic mutations in the same patient is unique and sheds light into the genetic mechanisms underlying disease severity and penetrance variability in ALPS.

Somatic FAS mutations—The second most common genetic cause of ALPS is somatic mutations in *FAS* [12,25]. These patients present with mutations in blood elements only, mostly affecting DNT cells and a small proportion (10-20%) of CD4, CD8, CD20 and CD34 (progenitor) cells. Given the low prevalence of mutant cells in total lymphocytes, these patients typically lack apoptosis defects as tested *in vitro*, and test negative for *FAS* mutations when evaluated in whole blood cells [12]. The clinical manifestations are similar to patients with germline *FAS* mutations.

Caspase-10 and FASLG mutations—*CASP10* mutations were found in 10 patients thus far [26,27](Koneti Rao, personnal comuncation). These mutations were heterozygous and caused defective apoptosis in lymphocytes and dendritic cells [27]. The clinical phenotype was indistinguishable from that of patients with *FAS* mutations. To date, only 4 ALPS patients with FAS ligand (*FASLG*) mutations have been reported [28-31], including one with systemic lupus erythematosus (SLE)-like disease

Treatment and prognosis

ALPS management aims to control autoimmune cytopenias and to monitor for lymphoma. In a recent study, 74% of the patients required medical and/or surgical treatment at some point in life, with the median age of onset of immunosuppression being 7.5 years. [5]. Initial management for ALPS-related autoimmune cytopenias is similar to sporadic cytopenias in other patient populations, including parenteral high dose methylprednisolone and high dose intravenous immunoglobulin [32]. Some patients with autoimmune neutropenias who experience associated infection may be treated with low dose granulocyte colony stimulating factor. In patients with refractory autoimmune cytopenias requiring chronic steroid therapy, mycophenolate mofetil has been shown to be an effective steroid-sparing agent that maintains adequate blood cell counts and reduces the need for other immunosuppressive agents or splenectomy [18, 32, 33]. Finally, some ALPS patients with hypersplenism and associated cytopenias have shown significant improvement following treatment with sirolimus [18, 34]. Spleen guards should be considered for ALPS patients with massive splenomegaly, to help reduce the risk of traumatic splenic rupture. These patients with very large spleens should be discouraged from participating in contact sports. All ALPS patients who are asplenic should be treated with long-term antibiotic prophylaxis against pneumococcal sepsis using penicillin V. Patients that who have undergone surgical splenectomy are encouraged to wear medical alert

Most ALPS patients are expected to live a normal life span with few clinical complications. Patients with mutations affecting the intracellular domain of the FAS protein have more severe disease and are at increased risk for Hodgkin and Non-Hodgkin B-cell lymphomas [4,15,35]. Patients with mutations affecting the extracellular domain of FAS have also been

reported to develop lymphomas, extending the spectrum of at-risk patients [5]. Although lymphoma is the most feared complication in ALPS, the most lethal complication is postsplenectomy sepsis. In a recent series, 6 out of 90 ALPS patients died over a 25 year follow up, being four of postsplenectomy infection, one of aplastic anemia and one of a stroke [5]. Based on these data, splenectomy is strongly disencouraged in ALPS.

ALPS-RELATED DISORDERS

There are several monogenic disorders that clinically resemble ALPS, but have distinctive findings that made them be classified separately. These entities are discussed below.

Caspase-8 deficiency

CASPASE-8 deficiency state (CEDS) is caused by autosomal recessive mutations in the gene encoding caspase-8 (*CASP8*). In 2002, Chun et al. described two siblings, a 12-yr-old female and an 11-yr-old male born to a distantly consanguineous family, with some features of the autoimmune lymphoproliferative syndrome (ALPS), such as lymphadenopathy, splenomegaly, slight elevation of the TCR$\alpha\beta^{+}CD4^{-}CD8^{-}$ T cells and defective lymphocyte apoptosis [36]. In addition, and unlike other ALPS patients, these patients also presented with mild recurrent sinopulmonary and cutaneous herpes simplex virus (HSV) infections [36]. The affected siblings carried homozygous mutations in the gene encoding caspase-8 (*CASP8*, p.R248W) associated with a combined immunodeficiency characterized by inverted CD4/CD8 ratios, slightly diminished IgG, IgA and IgM levels and poor responses to pneumococcal immunization. The authors noticed a defective activation of T, B and NK cells, underlying the immunodeficiency state.

Recently, two more patients from the same extended family have been identified (S. Rosenzweig and J. Oliveira, unpublished results). These patients had immunodeficiency, with recurrent sinopulmonary infections, warts, molluscum contagiosum, poor pneumococcal antibodies, and normal DNTs. Besides their splenomegaly and lymphocytosis, they also had accumulation of lymphocytes in multiple organs such as liver, spleen, lung, and brain. Patient 1 died from complications of a pulmonary transplant for interstitial lung disease of unknown etiology. Patient 2 died due to progressive pulmonary and neurological problems. The lymphocytic infiltration seen in these older patients is similar to the one seen in parenchymal organs of older mice lacking caspase-8 within their T cells [37]. Thus, CEDS in both humans and mice is characterized by a mild combined immunodeficiency with pronounced lymphocyte accumulation and infiltration but minimal autoimmunity.

Genetics and Pathophysiology—The clinical phenotype of immunodeficiency coupled to lymphoproliferation can be explained by the dual role of CASPASE-8 in signaling for both apoptosis and lymphocyte activation. Upon FAS death receptor stimulation, CASPASE-8 is recruited into the death-inducing signaling complex (DISC) for apoptosis induction. In contrast, upon immunoreceptor stimulation, CASPASE-8 assembles with the CARMA1-BCL10-MALT1 (CBM) and the IKKα/β complexes, activating the gene transcription factor NF-kB for lymphocyte activation [38,39].

FADD deficiency

Four related patients from a consanguineous family with FADD deficiency due to autosomal recessive mutations (p.C105W) were recently identified, who had an immunodeficiency phenotype [40]. The patients had invasive pneumococcal infections with functional hyposplenism, as well as repeated febrile episodes of encephalopathy with liver dysfunction that were associated with viral infections. One patient had increased DNT cells, a lymphocyte apoptosis defect, elevated biomarkers that are usually associated with ALPS-FAS, and DAT autoantibodies without reported autoimmune disease. Unlike CEDS or ALPS, none of the FADD-deficient patients had splenomegaly or lymphadenopathy. Taken together, FADD deficiency, like CEDS, clinically overlaps with ALPS but differs in featuring immunodeficiency prominently.

Pathophysiology—FADD has multiple roles as a signaling molecule [41]. It is an adapter molecule that links surface FAS to downstream caspases during apoptosis signaling (Figure 1), but can also associate with the CARMA1-BCL10-MALT1 complex (but not the IKKα/β complex) upon antigen receptor stimulation [38]. Additionally, it is also required for type I IFN antiviral immunity [42]. These different functions explain the broad phenotype of FADD deficient patients.

RAS-associated Autoimmune Leukoproliferative Disorder (RALD)

RALD patients have several clinical and laboratory features that overlap with ALPS [43-45]. They present with a generally mild degree of peripheral lymphadenopathy, significant splenomegaly, and autoimmunity including AIHA, ITP, and neutropenia age at ages varying from 1 to 47 years of life. In some patients, a history of recurrent mild upper and lower respiratory tract infections can be elicited [43]. Unlike ALPS, patients with RALD have transient or persistent elevation in granulocytes and monocytes. Some RALD patients have a clinical and laboratory phenotype very similar to juvenile myelomonocytic leukemia (JMML) early in life, with marked hepatosplenomegaly and monocytosis. However, unlike patients with JMML, the clinical outcome is chronic and benign [43-45].

Immunophenotyping in RALD reveals mild to no elevation in DNTs and an expansion of B cells. Total lymphocyte numbers can be normal or modestly decreased. In contrast, absolute or relative monocytosis is noted in all patients seen thus far. Autoantibodies are typically detected, including ANA, rheumatoid factor, anti-phospholipid, anti-cardiolipin anti-platelet, anti-neutrophil and/or anti-red blodd cell [43-45]. Serum soluble Fas ligand and vitamin B12 are normal, as well as *in vitro* FAS-induced apoptosis. By contrast, in RALD patients, the T cells are resistant to IL-2 withdrawal-induced cell death, pointing to a fundamentally different apoptotic defect [43-45]. The histopathological findings include nonspecific polyclonal plasmacytosis with reactive secondary follicles, but without the typical paracortical expansion caused by DNT cells seen in ALPS. Given the small number of patients diagnosed to date, it is not known whether these patients are at increased risk for hematological malignancy.

Genetics and Pathophysiology—RALD patients harbor somatic, gain-of-function mutations in *KRAS* or *NRAS*, which are present only in blood cells. These mutations disrupt

the interaction of RAS with GTPase-activating proteins (GAPs), diminishing its GTPase activity by over 300-fold and locking the molecule in activated position [46]. This permanent activation state increases cell signaling through the RAS-ERK pathway, inducing the phosphorylation and destruction of the pro-apoptotic protein BIM [47,48]. Consequently, the cells become resistant to certain kinds of apoptotic stimuli, such as growth-factor (IL-2) withdrawal. Additionally, persistent ERK signaling decreases the intracellular levels of negative inhibitors of the cell cycle, namely $p27^{kip1}$, allowing for increased proliferation in the face of limiting IL-2 levels [43]. Recent work has also suggested that adequate RAS signaling is important for B cell selection, potentially explaining the multiple antibody-mediated autoimmune manifestations seen in these patients [49,50].

PKCδ Deficiency

A novel benign lymphoproliferative disorder has been recently described in two patients from distinct ethnic backgrounds [51,52]. The patients presented with findings that resembled ALPS, such as chronic persistent splenomegaly, lymphadenopathy and autoimmune disorders, but did not fulfill criteria for this disease. The patient described by Kuehn et al. is a hispanic male with a clinical history including recurrent otitis with bilateral perforated tympanic membranes and sinusitis starting in early childhood [51]. He had persistent generalized lymphadenopathy and hepatosplenomegaly, accompanied by intermittent fevers starting at 3 years of age. Hepatosplenomegaly became very prominent by 5 years of age and marked mediastinal lymphadenopathy developed. He had an intermittent facial rash in a butterfly distribution and confluent erythematous macules over the trunk and extremities but no other evidence for vasculitis or glomerulopathy. Additionally, he had persistently detectable EBV copy numbers between 2000-8000 genomes/μl. These findings were reminiscent of the $PKC\delta^{-/-}$ mouse [53].

Laboratory evaluation revealed a slight leukocytosis, normochromic normocytic anemia and borderline thrombocytopenia presumed to be secondary to splenic sequestration [51]. ANA and ENAs were positive, and flow cytometry revealed B cell lymphocytosis with the majority of B cells expressing CD5, with a decrease in class switched B cell memory subsets. NK cell cytolytic activity was very diminished, with normal numbers of NK cells. Lymph node histology showed open sinuses, expansion of the B cell areas with prominent B-follicles with ill-defined germinal centers, lacking polarization, and prominent mantles. Typical histological features of ALPS were not observed. This patient was treated with rapamycin, with near complete resolution of the lymphadenopathy.

The patient described by Salzer et al. was a 12 year-old boy from Turkish origin who had a clinical history of mild recurrent infections (otitis, gastroenteritis, sinusitis and pneumonia) until the age of 4, when he was started on IVIG [52]. He had multiple autoimmune disorders such as membranous glomerulonepritis early in life, relapsing polychondritis, hypothyroidism, and anti-phospholipid syndrome. He presented generalized lymphadenopathy and hepatosplenomegaly since the age of 3 years. Laboratory findings included positive ANA, anti-dsDNA, anti-cardiolipin and anti-collagen 4 antibodies. IgG weas slightly below the inferior normal range, with normal IgA and IgM. In contrast to the patient described by Kuehn et al., his total B-cell numbers were decreased, with low class-

switched memory B cells and increased $CD21^{low}$ B cells. T cell immunophenotyping was normal. Lymph node histology demonstrated nonspecific reactive follicular hyperplasia, without ALPS features. The patient was initially treated with IVIG replacement for the infections and anti-CD20 for the autoimmunity. Lately, the patient has been treated with mycophenolate-mofetil and low dose steroids, with good disease control.

Genetics and Pathophysiology—Both patients harbored homozygous mutations in *PRKCD*, the gene encoding for the protein kinase C, isoform δ [51,52]. Protein kinase C (EC 2.7.11.13), also known as PKC, is a family of serine/threonine kinases that play a key role in the regulation of various cellular processes, including cell proliferation, apoptosis, and differentiation [54,55]. PKCδ has important roles in B cell signaling and autoimmunity, as well as regulation of growth, apoptosis, and differentiation of a variety of cell types [50,53-57]. The impressive lymphocyte accumulation seen in these patients could be explained by the excessive proliferation of the patient's B cells demonstrated ex vivo, as well as by defective B cell apoptosis [51]. Interestingly, Kuehn et al. also noticed a striking oversecretion of IL-10 by the patient's cultured B cells. As IL-10 is a B cell trophic factor, this could explain in part the cellular phenotype. The NK cell dysfunction reported serves as an explanation for the chronic, low grade EBV infection seen in one individual [51], but the role of PKCδ in NK cell function is currently unknown.

CONCLUSIONS

There is an ever-expanding group of human disorders characterized my marked benign lymphoproliferation and autoimmune phenomena. Despite their rarity, these monogenic disorders shed light into the role of specific proteins in human T cell proliferation, apoptosis and tolerance mechanisms.

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Bullets and annotations

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KEYPOINTS

- The autoimmune lymphoproliferative syndrome (ALPS) is characterized by non-malignant lymphocyte accumulation, blood-element directed autoimmunity and elevation of circulating $CD3^{+}TCR\text{-}\alpha\beta^{+}CD4^{-}CD8^{-}$ cells.
- RAS-associate autoimmune leukoproliferative disease (RALD) is caused by somatic mutations in NRAS or KRAS, and manifested clinically by splenomegaly, mild lymphadenopathy, autoimmune phenomena and relative or absolute monocytosis.
- Caspase-8 deficiency presents with findings of ALPS, such as mild lymphocyte accumulation, but also with a cellular immune deficiency, with defective function of T, B and NK cells.
- FADD deficiency has been reported in only one family thus far, and presents mostly with as an immune deficiency, with recurrent bacterial and viral infections.
- PKCδ deficiency is the newest addition to the group, and patients present with important lymphadenopathy and splenomegaly, autoimmune phenomena and clinical signs of NK cell deficiency, such as chronic EBV infection.

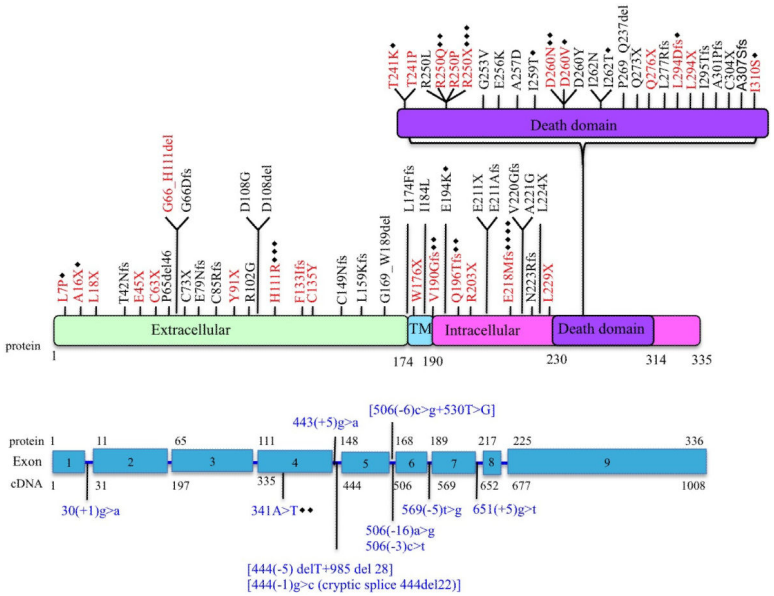

Fig 1.

Schematic representation of FAS mutations in ALPS patients. TM, transmembrane. Red text indicates mutations evaluated in this study. Blue text indicates complex mutations. Black diamonds represents the number of families with same mutation. Reproduced with permission from reference [18].

Table 1

Diagnostic criteria for ALPS based on International ALPS Workshop 2009.

Revised diagnostic criteria for ALPS based on First International ALPS Workshop 2009
Required criteria
1. Chronic (> 6 months), nonmalignant, noninfectious lymphadenopathy and/or splenomegaly
2. Elevated $CD3^+$ $TCR\alpha\beta^+CD4^-$ $CD8^-$ DNT cells (> 1.5% of total lymphocytes or > 2.5% of $CD3^+$ lymphocytes) in the setting of normal or elevated lymphocyte counts
Additional criteria
Primary
1. Defective lymphocyte apoptosis in 2 separate assays
2. Somatic or germline pathogenic mutation in FAS, FASLG, or CASP10
Secondary
3. Elevated plasma sFASL levels (> 200 pg/mL), plasma IL-10 levels (> 20 pg/mL), serum or plasma vitamin B_{12} levels (> 1500 ng/L) or plasma IL-18 levels > 500 pg/mL
4. Typical immunohistologic findings as reviewed by a hematopathologist
5. Autoimmune cytopenias (hemolytic anemia, thrombocytopenia, or neutropenia) with elevated IgG levels (polyclonal hypergammaglobulinemia)
6. Family history of a nonmalignant/noninfectious lymphoproliferation with or without autoimmunity
Definitive diagnosis: Both required criteria plus one primary accessory criterion.
Probable diagnosis: Both required criteria plus one secondary accessory criterion. Treat as ALPS until genetics can be done.
Adapted from [4]