Taylor & Francis
Taylor & Francis Group

CURRENT CLINICAL PRACTICE

Causes and consequences of the autoimmune lymphoproliferative syndrome

V. KONETI RAO & STEPHEN E. STRAUS

Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Building 10, Room 11-N228, 10 Center Drive, Bethesda MD 20892-1888, USA

Abstract
Autoimmune lymphoproliferative syndrome (ALPS) is the first autoimmune hematological disease whose genetic basis has been defined. It is a disorder of apoptosis in which the inability of lymphocytes to die leads to lymphadenopathy, hypersplenism, and autoimmune cytopenias of childhood onset. More than 200 ALPS patients have been studied over the last 15 years and followed by our colleagues and ourselves at the Clinical Center of the National Institutes of Health. Based upon this experience we have determined that patients with germline mutations of the intracellular domain of Fas protein, the most frequent single genetic cause of ALPS, have a significantly increased risk of developing Hodgkin and non-Hodgkin lymphoma (NHL), underscoring the critical role played by cell surface receptor-mediated apoptosis in eliminating redundant proliferating lymphocytes with autoreactive and oncogenic potential. The major determinants of morbidity and mortality in ALPS are the severity of the autoimmune disease, hypersplenism, asplenia-related sepsis, and the risk of lymphoma, which in itself requires long-term surveillance. Though most episodes of cytopenias respond to courses of conventional immunomodulatory agents, some ALPS patients, especially those with massive splenomegaly and hypersplenism, may require splenectomy and/or ongoing immunosuppressive treatment. Thus, ALPS highlights the importance of cell death pathways in health and disease.

Keywords: *Apoptosis, autoimmune cytopenias, ITP, AIHA, AIN, splenomegaly, lymphoproliferation*

Introduction

The autoimmune lymphoproliferative syndrome (ALPS) is the first human immune disorder to be associated with defective lymphocyte apoptosis leading to accumulation of lymphoid mass and persistence of autoreactive cells as prominent non-malignant lymphadenopathy and hepatosplenomegaly [1,2]. Many ALPS patients present to a hematologist in early childhood for further assessment and management of otherwise inexplicable autoimmune hemolytic anemia (AIHA), thrombocytopenia (ITP) and/or neutropenia and, in that background, some of them develop B-cell lymphoma.

Molecular pathogenesis of ALPS

Autoimmunity results from failure of self-tolerance, which can be further divided into central and peripheral tolerance. Central tolerance is fostered by apoptosis through elimination of unnecessary and immature effector cells in generative lymphoid organs (the bone marrow and thymus); while mechanisms of peripheral tolerance include anergy, deletion by apoptosis and suppression by regulatory T cells to avoid autoimmunity and tissue damage [3]. Apoptosis, the intrinsic death program of cells, is triggered by any of several effector molecules either through receptor-ligand interactions at the cell surface (the extrinsic pathway) or by the induction of

Correspondence: V. K. Rao, Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Building 10, Room 11-N228, 10 Center Drive, Bethesda MD 20892-1888, USA. Tel: 1 301 496 6502. Fax: 1 301 496 7383.E-mail: koneti@nih.gov

mitochondrial enzymes (the intrinsic pathway). Lymphocyte apoptosis mediated by the cell surface receptor Fas plays a pivotal role in the termination of redundant immune responses. Originally characterized from a human diploid fibroblast cell line as the FS-7 associated surface antigen [4], Fas (also termed CD95 and APO-1) is a member of the tumor necrosis factor (TNF) receptor superfamily of proteins that directly trigger receptor mediated apoptosis to maintain lymphocyte homeostasis, peripheral immune tolerance and prevent autoimmunity. It is a membrane bound molecule that is highly expressed on activated B and T lymphocytes. Conformational change of Fas leading to its trimerization by the binding of FasL or agonistic antibodies triggers the rapid recruitment of the death domain (DD) of the adaptor protein FADD (Fas-associated death domain) to the homologous DD in the cytoplasmic tail of Fas. This is followed by the recruitment of procaspases 8 or 10 through the interaction of their death-effector domains with the amino termini of FADD. The resulting Fas/FADD/-caspase complex is termed the death-inducing signaling complex (DISC) that incites a further cascade of caspase activation culminating in the death of cells [5–7].

The essential role that Fas exerts in maintaining lymphocyte homeostasis and peripheral immune tolerance to prevent autoimmunity was first elucidated by studies in Fas-deficient MRL/lpr − /− mice. Mice homozygous for Fas mutations develop hypergamma-globulinemia, glomerulonephritis, massive lymphade-nopathy and expansion of an otherwise rare and unique population of TCR αβ cells that lack expression of both CD4 and CD8, and hence are known as double-negative (DN) T cells [6–8]. This provided insights into the pathophysiology of a similar syndrome being observed in humans [8–10].

ALPS, as this disorder was subsequently named, has been shown to represent a failure of apoptotic mechanisms. It is most often associated with hetero-zygous mutations in the gene encoding the Fas protein, *TNFRSF6* (tumor necrosis factor receptor superfamily 6), and other related effector proteins that regulate lymphocyte survival. Most of these mutations are inherited in an autosomal dominant fashion with variable penetrance. The likelihood that an individual who carries a Fas mutation will manifest ALPS appears to depend on several factors, only some of which are known at this time [11,12].

Diagnosis of ALPS

Case definition and classification

Criteria for the diagnosis of ALPS have been defined and appear to be highly sensitive and specific and explain a number of previously observed idiopathic clinical syndromes (Table I). Chronic lymphadeno-pathy and organomegaly simulating lymphoma has been recognized as a distinct clinical entity for nearly 40 years [13]. The clinical features of ALPS, as they are now understood, are due to the accumulation of lymphoid mass and persistence of autoreactive cells with an increase in characteristic circulating DNT cells.

Diagnostic criteria for ALPS include: chronic, non-malignant lymphadenopathy and/or splenomegaly persisting for at least 6 months; defective (less than half normal) Fas-mediated lymphocyte apoptosis as assayed *in vitro*; and elevated ($\geq 1\%$ or $\geq 20/\mu l$) circulating CD4-/CD8-DNT cells expressing the αβ T-cell receptor above their normal range of $0.1-0.9\%$ of all lymphocytes (with absolute counts exceeding $2-17/\mu l$) (Figure 1). Molecular studies have revealed that germline heterozygous mutations in the genes encoding apoptosis signaling proteins Fas, Fas ligand (FasL), Caspase 8, or Caspase 10 are present in most patients of ALPS [14–16]. Mutations in the gene encoding Fas alone account for approximately 75% of all individuals with ALPS [2]. Currently patients are classified as ALPS Type Ia and Ib when they carry a mutation of the Fas and FasL gene, respectively, ALPS Type II when the patient carries a Caspase 10 or Caspase 8 gene mutation, and ALPS Type III when no mutation can be identified (Table II). More recently a subgroup of ALPS patients were also noted to have somatic mutations of Fas specifically detected in isolates of characteristic DNT lymphocytes [17,18]. Diagnostic work up includes evaluation of proband and family members through clinical and laboratory testing for required features of ALPS (Table I), which consists of immunophenotyping of peripheral blood for enumeration of DNT cells and *in vitro* apoptosis assay as well as detailed molecular genetic analysis for mutations in apoptosis pathway genes implicated in ALPS: Fas, Fas-ligand, and Caspases 10 and 8.

Table I.   Criteria for the diagnosis of ALPS.

Required features

1.   Chronic non-malignant lymphadenopathy, splenomegaly, or both

2.   Increase in circulating double negative T (DNT) cells that are CD4 − CD8 − and express the alpha/beta T-cell receptor above the normal range of 0.1–0.9% of lymphocytes (absolute counts range normally from 2 to 17/μl)

3.   Demonstration of defective antigen-induced lymphocyte apoptosis on *in vitro* culture

Supporting features

1.   Family history of autoimmune lymphoproliferative syndrome

2.   Typical findings on histopathologic analysis of lymph node or splenic tissue

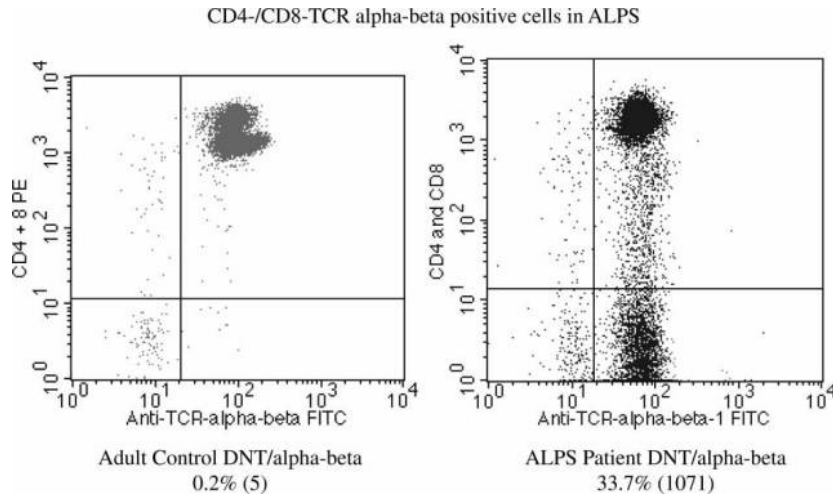3.   Mutations of genes encoding Fas or related apoptosis signaling proteins

Figure 1. Periphreal blood immunophenotyping showing elevated (≥1% or ≥20/ul) circulating CD4-/CD8-DNT cells expressing the αβ T-cell receptor. ([1,24], See text for details).

Clinical features of ALPS

Prominent non-malignant lymphadenopathy in ALPS arises typically in early childhood and is often accompanied by hepatosplenomegaly and auto-immune cytopenias of one or more lineages. Lymphadenopathy and splenomegaly may be massive and distort anatomic landmarks, frequently affecting the neck and axillary regions and persist for two or more years [19]. Enlargement of abdominal and thoracic lymph nodes are also often noted by ultrasound and/or computerized tomography [20]. Splenomegaly may also manifest as cytopenias secondary to cellular sequestration due to hypersplenism. The clinical and laboratory features of ALPS do not appear to differ markedly between patients who have identified mutations and those who do not [2,19]. Several non-hematological autoimmune diseases have also been reported in association with ALPS including Guillian-Barré syndrome, glomerulonephritis, uveitis and autoimmune liver disease (Table III).

Presentation of children with generalized adenopathy, splenomegaly and autoimmue mutilineage cytopenias represents a diagnostic challenge because their clinical and laboratory features overlap with and may manifest as those of other childhood hematological disorders including lymphoma, hereditary spherocytosis, Evans Syndrome [21] and Rosai–Dorfman Disease [22]. Other immunological disorders associated with autoimmune phenomena that must be differentiated from ALPS include common variable immunodeficiency, Wiskott–Aldrich syndrome, interleukin (IL)-2 receptor α-chain deficiency and the X-linked immunodysregulation–polyendocrinopathy–enteropathy (IPEX) syndrome.

Table III. Demographics and Clinical features in 79 patients with autoimmune lymphoproliferative syndrome. Modified from Sneller et al. 2003 [19].

Gender	Female 43 Male 36
Race	White 69 Black 6 Other 4
Median age at presentation (range)	2 years (birth–15 years)
Manifestation, Patients, n (%)	
Lymphoproliferative disease	79 (100)
Splenomegaly	75 (95)
Lymphadenopathy	76 (96)
Hepatomegaly	57 (72)
Lymphoma	7 (9)
Autoantibodies★	64 (81)
Any Autoimmune disease:	37 (47)
Hemolytic anemia†	23 (29)
Idiopathic thrombocytopenic purpura	18 (23)
Neutropenia	15 (19)
Glomerulonephritis	2 (3)
Optic neuritis or uveitis	2 (3)
Guillian-Barre Ç syndrome	1 (1)
Primary biliary cirrhosis	1 (1)
Coagulopathy/Factor VIII inhibitor	1 (1)

Data compiled from probands and relatives with ALPS (47 discrete families).
★ 30 patients had one or more autoantibodies but no overt autoimmune disease.
† The Direct Coombs test was positive for both IgG and C3d in all patients with hemolytic anemia.

Table II. NIH ALPS Cohort (N = 200).

Gene	Type	N
Fas (*TNFRSF6*)	Ia	125
Fas Ligand (*TNFSF6*)	Ib	1
Caspase 10	IIa	4
Caspase 8	IIb	2
Unknown	III	50
Unknown	Phenotype★	18

★ Patients who do not have all 3 required features for the diagnosis of ALPS but in whom chronic lymphoproliferation and autoimmunity are prominent are categorized as having the ALPS phenotype.

Laboratory findings in ALPS

Lymphocyte dysregulation in ALPS. Lymphocyte dysregulation in ALPS is revealed by an elevated percentage of DNT cells in the peripheral blood, bone marrow, spleen and lymphoid tissues of patients producing a fairly characteristic histopathological picture [23,24]. Lymph node biopsy often shows both follicular hyperplasia and paracortical expansion with a mixed infiltrate containing TCRα/β DNT cells, a feature unique to ALPS, and helps to distinguish this syndrome from other benign and malignant lymphoproliferative lesions (Figure 3). Study of lymph node tissue for clonality through immunoglobulin and T-cell receptor gene rearrangements as well as cytogenetic evaluation for chromosomal aneuploidy are important to help diagnose lymphoma in patients with a background of chronic lymphadenopathy and other features resembling ALPS. Patients with ALPS also demonstrate a lymphocytosis with a skewed Th-2 pattern of immune responses, one manifestation of which is elevated circulating and tissue interleukin-10 (IL-10) levels [25].

Other associated abnormalities noted in peripheral blood, bone marrow. Features of ALPS include hypergammaglobulinemia and circulating autoantibodies, most commonly manifesting as Coomb's direct antiglobulin test (DAT) positive hemolytic anemia, autoimmune thrombocytopenia and neutropenia [26–28]. Eosinophilia [29] and monocytosis are frequent findings in ALPS patients. Bone marrow showing some degree of dyserythropoiesis [30] and depleted iron stores are also not uncommon.

In vitro apoptosis defect. All patients with ALPS, by definition, exhibit defective lymphocyte apoptosis assayed *in vitro* by specialized laboratories using peripheral blood lymphocytes cultured in the presence of IL-2 for a few days and stimulated with phytohemagglutinin. Apoptosis is induced in these assays by a monoclonal antibody that binds to activated-Fas on the lymphocyte cell surface. The majority of cells from normal controls are killed, while lymphocytes from patients with clinical features of ALPS are relatively spared [31,32] (Figure 2).

Natural history: Hypersplenism, lymphadenopathy, autoimmune cytopenias and lymphoma transformation

The first clinical expression of ALPS may be recognized by the pediatrician as chronically enlarged lymph nodes and spleen in infants who are otherwise asymptomatic. However, a large proportion of patients eventually proven to have ALPS may present initially with episodes of pallor and icterus associated with hemolytic anemia, spontaneous bruises and mucocutaneous hemorrhages due to thrombocytopenia or bacterial infections associated with neutropenia. The potential for multiple autoimmune diseases involving different organ systems such as uveitis, hepatitis, glomerulonephritis, and encephalomyelitis
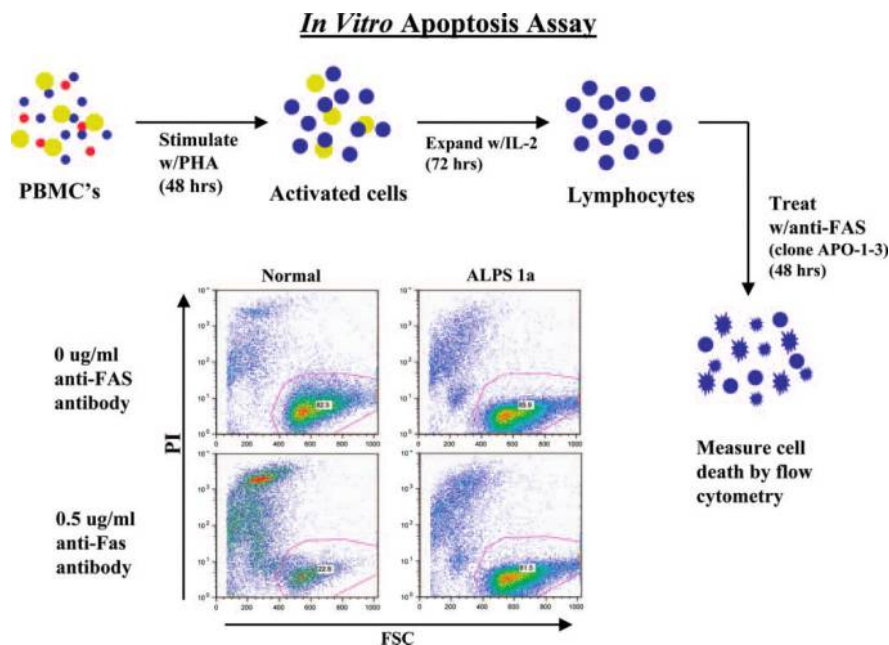

Figure 2.   Defective (less than half normal) Fas-mediated lymphocyte apoptosis as assayed *in vitro* using peripheral blood lymphocytes cultured in the presence of IL-2 for a few days and stimulated with phytohemagglutinin. Apoptosis is induced in these assays by a monoclonal antibody that binds to activated-Fas on the lymphocyte cell surface. PI—Propidium Iodide stain for dead cells; FSC along *X*-axis shows persistent FAS negative live cells in ALPS patient ([31,32], see text for details).
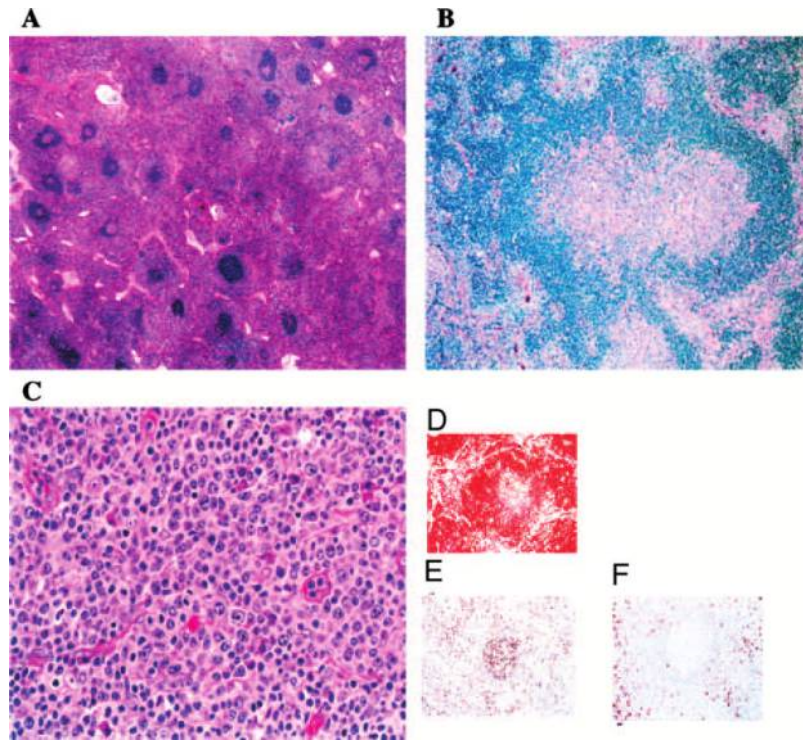
Figure 3.   Lymph node biopsy (H&E and immunohistochemical stains) showing both follicular hyperplasia and paracortical expansion with a mixed infiltrate containing DNT cells, a feature most evident in patients with ALPS Type Ia. Histopathology of lymph nodes. A: The paracortex is markedly expanded by lymphocytes with pale pink cytoplasm. Primary and secondary follicles are numerous. Some follicles show regressive changes (upper right). H&E; original magnification, × 100. B: Progressive transformation of germinal centers was a focal but relatively frequent finding. H&E; original magnification, × 200. C: The paracortex is populated by lymphocytes, plasma cells, and immunoblasts. Note frequent mitotic figures. H&E; original magnification, × 600. Lymph node demonstrates paracortical expansion by CD3 + DN T cells. Immunoperoxidase stains (ABC immunoperoxidase technique, hematoxylin counterstain; original magnification, × 200) performed in paraffin sections demonstrates expansion of interfollicular regions by CD3 + T cells (D) that are largely CD4 − (E) and CD8 − (F). Most CD4 + cells are within germinal centers. (Modified from Lim et al.: Histopathology of ALPS Lymph node [24]).

in a single patient with ALPS is being recognized increasingly as patients are followed for many years.

The median age of initial presentation with florid lymphadenopathy and splenomegaly is about 24 months. The extent of adenopathy and splenomegaly may decrease through adolescence. Similarly, clinical manifestations of refractory, chronic cytopenias are most severe in childhood; however symptoms related to cytopenias can first appear at any age.

Genetic counseling is an integral part of the evaluation of a family with one or more ALPS patients. Assessment of relatives of ALPS probands with mutations in genes encoding Fas or caspase 10 usually identifies a parent, sibling or a more distant relative with identical heterozygous mutations inherited in an autosomal dominant fashion. Many such subjects manifest few if any clinical features of ALPS, although they all share *in vitro* apoptosis defects. Elevation in DN T cell numbers and IL-10 levels are typically not present in the absence of the clinical stigmata of ALPS [33]. Patient and family members are educated to seek timely help for any systemic symptoms, cytopenias, unexpected fluctuations in lymph node and spleen size. Patients with mutations involving the intracellular death domain of the Fas

molecule are significantly more likely than ones with extracellular domain mutations to manifest ALPS features and they have more severe clinical phenotypes.

ALPS patients with germline mutation of the intracellular domain of Fas have a significantly increased (14 and 51-fold) risk of developing non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) [34,35], respectively, underscoring the critical role played by receptor-mediated apoptosis in eliminating proliferating lymphocytes with oncogenic potential. Among the cohort of 200 patients seen at NIH, 11 have developed lymphomas (6 Hodgkins and 5 B-cell NHL) with a median age of presentation with lymphoma of 17 years (range 2–50 years). More recently *TNFRSF6* gene encoding Fas was proposed to act as a tumor suppressor as it is silenced in many tumors [36]. In one report 20% of B-cell lymphomas derived from (post) germinal center B-cells carried somatic mutations in the exon 9 of this gene, which encodes the Fas intracellular death domain [37].

Inherited *CASP10* gene mutations also underlie defective lymphocyte and dendritic cell apoptosis in some patients with ALPS. CASP10 gene was analyzed for the detection of somatic mutations in 117 human

NHLs in one recent study. Overall, 17 NHLs (14.5%) were found to have CASP10 mutations. When the tumor-derived caspase 10 mutants were expressed in cells, apoptosis was suppressed. These data suggest that the inactivating mutations of the CASP10 gene might lead to the loss of its apoptotic function and contribute to the pathogenesis of some cases of NHL [38].

Management of lymphoproliferation and hypersplenism

Although massive adenopathy in growing children can incite considerable anxiety and may be socially isolating, treatment is not specifically indicated to reduce lymph nodes for cosmetic reasons alone. Neither corticosteroids nor immunosuppressive drugs like azathioprine, cyclosporin or mycophenolate mofitil reliably shrink the spleen or lymph nodes in patients with ALPS. Though the use of Fansidar first initiated for pneumocystis carinii prophylaxis was reported in a small series of patients with ALPS and ALPS-like conditions to be associated with reductions in lymphoproliferation [39], our experience with this drug as well as its active component pyrimethamine has failed to show regression of adenopathy or splenomegaly.

Approximately half of the 200 ALPS patients being followed in our clinic have had a splenectomy in order to manage recurring and chronic cytopenias, nearly 75% of who achieved long-term remission. However, five asplenic ALPS patients have had fatal opportunistic infections and many others have presented with pneumococcal sepsis following splenectomy. Thus, splenectomy should be avoided unless it is the only remaining measure to control chronic, refractory, life-threatening cytopenias. Spleen-guards made of fiberglass have been used with apparent success in protecting active children with large spleens from splenic rupture, allowing them to participate in usual school sports programs.

Asplenia care in ALPS patients

Asplenic ALPS patients require vigilance for septicemia due to pneumococcal bacteremia, which can be fatal, and has been in some of our patients. We have found that ALPS patients may be unable to mount or sustain protective levels of antibodies directed against pneumococcal polysaccharide antigens following vaccination. Based upon our experience, we advise that all asplenic ALPS patients be maintained on long-term antibiotic prophylaxis against pneumococal sepsis using penicillin V or fluoroquinolones. We further advise our asplenic patients to wear alert bracelets; we also educate them and their parents about the importance of seeking medical care promptly for a significant febrile illness requiring IV antibiotics until bacterial sepsis is ruled out.

Our recommendations also include maintenance of daily antibiotic prophylaxis as well as periodic surveillance and reimmunization against pneumococci using a combination of both 7-valent conjugate (Prevnar) and 23-valent polysaccharide (Pneumovax) vaccines [40].

Treatment of ALPS related cytopenias:

The initial management of patients with ALPS-related autoimmune cytopenias (AIHA, ITP, AIN) is similar to that used for immune cytopenias in other patient populations:

1. Immune-suppression with corticosteroids: High-dose pulse therapy with IV methylprednisolone (5–30 mg/kg) followed by low-dose oral prednisone (1–2 mg/kg) maintenance that can often be successfully tapered over several months.
2. IVIG (1–2 g/kg) given concomitantly with pulse dose methylprednisolone (30 mg/kg × 1–2 days) may benefit some patients with severe AIHA by abrogating antibody-mediated red cell destruction and allowing packed red blood cell (PRBC) transfusion support for severe anemia.
3. Some ALPS patients with chronic neutropenia and associated infections benefit from thrice weekly, low-dose (1–2 μg/kg SQ) G-CSF.
4. In addition to a case report of successful use of Rituximab and Vincristine in a single patient with ALPS [41], standard dose Rituximab (375 mg/M^2/week × 4) for refractory, chronic cytopenias has been used in 5 ALPS patients in NIH-CC cohort with durable responses noted in two of them.
5. Some patients, especially those with massive splenomegaly and hypersplenism, may prove refractory to standard drug regimens and PRBC transfusions and require ongoing chronic, long term immune-suppression. Recently, we described the successful use of Mycophenolate mofetil (MMF; 600 mg/M^2/dose twice daily) for cytopenias in 13 children with ALPS. Twelve responded to MMF for a median follow-up of 49 weeks (range 38–240 weeks), as defined by maintenance of adequate blood counts and reduction in dosage or cessation of other immunosuppressive agents.. In some patients, MMF may have allowed splenectomy to be avoided or postponed until the very young children had aged and would better tolerate asplenia. This preliminary experience suggests that MMF may spare chronic steroid usage in patients with ALPS-associated cytopenias [42].

Surveillance for lymphoma

Chronic adenopathy in ALPS patients can fluctuate over time and create some concern of evolving

lymphoma if one or more nodes enlarge unusually. Hence these patients need close clinical observation and serial CT scans, while some undergo repeated biopsies. Most ALPS patients with lymphoma respond to conventional multi-agent chemotherapy and radiation. They present additional diagnostic challenges once therapy is discontinued as ALPS associated adenopathy recurs and must be distinguished from relapsing lymphoma. Non-invasive tests are desirable in ALPS to help determine if a biopsy is warranted and which of many enlarged nodes will likely yield informative tissue. Positron emission tomography (PET) using [^{18}F] fluoro-2-deoxy-D-glucose (FDG) uptake, as a measure of cellular glucose metabolism, has become a standard in the staging and follow up evaluation of cancers, including lymphomas [43,44]. We have undertaken a formal, prospective study in which we are exploring the potential value of whole body FDG–PET scan to determine whether qualitative or quantitative FDG localization can help differentiate ALPS patients with benign, albeit prominent, adenopathy from those with ALPS-associated lymphomas.

Role of allogeneic BMT in ALPS

The short-term prognosis of most of the patients with ALPS appears to be very good. The chronic cytopenias seen in many ALPS patients may improve with age and does continue to respond to conventional immunosuppressive treatment. Thus, there is no need to entertain allogeneic stem cell transplantation in many patients with ALPS. Stem cell transplantation has been successful in patients with very severe and refractory cytopenias [45,46]. Of course, a sibling who carries the same apoptosis mutation as the proband is not an appropriate marrow donor. Mortality due to matched unrelated donor derived allogenic BMT is too high (35–45%) to justify this procedure for the vast majority of patients with a chronic disease like ALPS in which a near normal lifespan can otherwise be expected. At present, stem cell transplantation should be reserved for those ALPS patients with a severe phenotype, such as that associated with the rare occurrence of a homozygous Fas mutation [47–49].

Future directions and implications of ALPS

The major determinants of morbidity and mortality in ALPS depend on the severity of the autoimmune disease, hypersplenism and asplenia related sepsis as well as development of lymphoma. Novel and non-toxic therapeutic interventions are necessary to control the lymphoproliferative process in patients with ALPS who have chronic lymphadenopathy and splenomegaly. However, patients with mutations abrogating function of the intracellular domain of the Fas protein are at risk of developing lymphomas and they need diligent long-term surveillance through monitoring of their adenopathy. Paradigms derived from managing a large cohort of patients with a rare disease like ALPS may also help 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 [50].

References

[1] Sneller MC, Wang J, Dale JK, Strober W, Middelton LA, Choi Y, et al. Clinical, immunologic, and genetic features of an autoimmune lymphoproliferative syndrome associated with abnormal lymphocyte apoptosis. Blood 1997;89:1341–1348.

[2] Straus SE, Sneller M, Lenardo MJ, Puck JM, Strober W. An inherited disorder of lymphocyte apoptosis: the autoimmune lymphoproliferative syndrome. Ann Intern Med 1999; 130:591–601.

[3] Rioux JD, Abbas AK. Paths to understanding the genetic basis of autoimmune disease. Nature 2005 Jun 2;435(7042): 584–589.

[4] Yonehara S, Ishii A, Yonehara M. A cell-killing monoclonal antibody (anti-Fas) to a cell surface antigen co-downregulated with the receptor of tumor necrosis factor. J Exp Med 1989;169(5):1747–1756.

[5] Lenardo MJ. Introduction: The molecular regulation of lymphocyte apoptosis. Sem in Immunol 1997;9:1–5.

[6] Debatin K, Stahne K, Fulda S, et al. Apoptosis in hematological disorders. Sem in Cancer Biol 2003;:149–158.

[7] Siegel RM, Muppidi JR, Sarker M, Lobito A, Jen M, Martin D, Straus SE, Lenardo MJ. SPOTS: Signaling protein oligomeric transduction structures are early mediators of death receptor-induced apoptosis at the plasma membrane. J Cell Biol 2004;167:735–744.

[8] Watanabe-Fukunaga R, Brannan CI, Copeland NG, Jenkins NA, Nagata S:. Lymphoproliferation disorder in mice explained by defects in Fas antigen that mediates apoptosis. Nature 1992;356:314–317.

[9] Cohen PL, Eisenberg RA:. Lpr and gld: Single gene models of systemic autoimmunity and lymphoproliferative disease. Ann Rev Immunol 1991;9:243–269.

[10] Sneller MC, Straus SE, Jaffe ES, Jaffe JS, Fleisher TA, Stetler-Stevenson M, et al. A novel lymphoproliferative/autoimmune syndrome resembling murine lpr/gld disease. J Clin Invest 1992;90:334–341.

[11] Fisher GH, Rosenberg FJ, Straus SE, Dale JK, Middleton LA, Lin AY, et al. Dominant interfering Fas gene mutations impair apoptosis in a human autoimmune lymphoproliferative syndrome. Cell 1995;81:935–946.

[12] Rieux-Laucat F, Blachere S, Danielan S, De Villartay JP, Oleastro M, Solary E, Bader-Meunier B, Arkwright P, Pondare C, Bernaudin F, Chapel H, Nielsen S, Berrah M, Fischer A, Le Deist F. Lymphoproliferative syndrome with autoimmunity: A possible genetic basis for dominant expression of the clinical manifestations. Blood 1999;94:2575–2582.

[13] Canale VC, Smith CH. Chronic lymphadenopathy simulating malignant lymphoma. J Pediatr 1967;70:891–899.

[14] Wang J, Zheng L, Lobito A, Chan FK, Dale J, Sneller M, et al. Inherited human Caspase 10 mutations underlie defective lymphocyte and dendritic cell apoptosis in autoimmune lymphoproliferative syndrome type II. Cell 1999;98:47–58.

[15] Chun HJ, Zheng L, Ahmad M, Wang J, Speirs CK, Siegel RM, Dale JK, Puck J, Davis J, Hall CG, Skoda-Smith S, Atkinson TP, Straus SE, Lenardo MJ. Pleiotropic defects in lymphocyte activation caused by caspase-8 mutations lead to human immunodeficiency. Nature 2002;419:395–399.

[16] van der Werff ten Bosch JE, Otten J, Thielemans K. Autoimmune lymphoproliferative syndrome type III: An indefinite disorder. Leuk lymphoma 2001;41:55–65.

[17] Puck JM, Straus SE. Somatic mutations — not just for cancer anymore (Perspective). NEJM 2004;351:1388–1390.

[18] Holzelova E, Vonarbourg C, Stolzenberg MC, et al. Autoimmune lymphoproliferative syndrome with somatic Fas mutations. NEJM 2004;351:1409–14194.

[19] Sneller MC, Dale JK, Straus SE. Autoimmune lymphoproliferative syndrome. Curr Opin Rheumatol 2003;15:417–421.

[20] Avila NA, Dwyer AJ, Dale JK, Lopatin UA, Sneller MC, Jaffe ES, et al. Autoimmune lymphoproliferative syndrome: A syndrome associated with inherited genetic defects that impair lymphocytic apoptosis — CT and US features. Radiology 1999;212:257–263.

[21] Teachey DT, Manno CS, Axsom KM, Andrews T, Choi JK, Greenbaum BH, McMann JM, Sullivan KE, Travis SF, Grupp SA. Unmasking Evans syndrome: T cell phenotype and apoptotic response reveal autoimmune lymphoproliferative syndrome (ALPS). Blood 2005;105:2443–2448.

[22] Maric I, Pittaluga S, Dale JK, Niemela JE, Delsol G, Diment J, Rosai J, Raffeld M, Puck JM, Straus SE, Jaffe E. Histologic Features of Sinus Histiocytosis With Massive Lymphadenopathy in Patients With Autoimmune Lymphoproliferative Syndrome. Am J Surg Pathol 2005 Jul;29(7):903–911.

[23] Bleesing JJ, Brown MR, Straus SE, Dale JK, Siegel RM, Johnson M, Lenardo MJ, Puck JM, Fleisher TA. Immunophenotypic profiles in families with autoimmune lymphoproliferative syndrome. Blood 2001;98:2466–2473.

[24] Lim MS, Straus SE, Dale JK, Fleisher TA, Stetler-Stevenson M, Strober W, et al. Pathological findings in human autoimmune lymphoproliferative syndrome. Am J Pathol 1998;153:1541–1550.

[25] Fuss IJ, Strober W, Dale JK, Fritz S, Pearlstein GR, Puck JM, et al. Characteristic T helper 2 T cell cytokine abnormalities in autoimmune lymphoproliferative syndrome, a syndrome marked by defective apoptosis and humoral autoimmunity. J Immunol 1997;158:1912–1918.

[26] Stroncek DF, Carter LB, Procter JL, Dale JK, Straus SE. RBC autoantibodies in autoimmune lymphoproliferative syndrome. Transfusion 2001;41:18–23.

[27] Kwon SW, Procter J, Dale JK, Straus SE, Stroncek DF. Neutrophil and platelet antibodies in autoimmune lymphoproliferative syndrome. Vox Sang 2003;85:307–312.

[28] Fang BS, Sneller MC, Straus SE, Frenkel L, Dale JK, Rick ME. Report of a factor VIII inhibitor in a patient with autoimmune lymphoproliferative syndrome. Am J Hematol 2000;64:214–217.

[29] Aspinall AI, Pinto A, Auer IA, Bridges P, Luider J, Dimnik L, et al. Identification of new Fas mutations in a patient with autoimmune lymphoproliferative syndrome (ALPS) and eosinophilia. Blood Cells Mol Dis 1999;25:227–238.

[30] Bader-Munier B, Rieux-Laucat F, et al. Dyserythropoiesis associated with a fas-deficient condition in childhood. Br J Hematol 2000;108:300–304.

[31] Jackson CE, Puck JM. Autoimmune lymphoproliferative syndrome, a disorder of apoptosis. Curr Opin Pediatr 1999;6:521–527.

[32] Fisher GH, Rosenberg FJ, Straus SE, Dale JK, Middleton LA, Lin AY, et al. Dominant interfering Fas gene mutations impair apoptosis in a human autoimmune lymphoproliferative syndrome. Cell 1995;81:935–946.

[33] Lopatin U, Yao X, Williams RK, Bleesing JJ, Dale JK, Wong D, Teruya-Feldstein J, Fritz S, Morrow MR, Fuss I, Sneller MC, Raffeld M, Fleisher TA, Puck JM, Strober W, Jaffe ES, Straus SE. Increases in circulating and lymphoid tissue interleukin-10 in autoimmune lymphoproliferative syndrome are associated with disease expression. Blood 2001 May 15;97(10):3161–3170.

[34] Straus SE, Jaffe ES, Puck JM, Dale JK, Elkon KB, et al. The development of lymphomas in families with Autoimmune Lymphoproliferative Syndrome (ALPS) with germline Fas mutations and defective lymphocyte apoptosis. Blood 2001;98:194–200.

[35] Poppema S, Maggio E, van den Berg A. Development of lymphoma in ALPS and its relationship to Fas gene mutations. Leuk Lymphoma 2004;45:423–431.

[36] Muschen M, Warskulat U, Beckmann MW. Defining CD95 as a tumor suppressor gene. J Mol Med 2000;78:312–325.

[37] Muschen M, Re D, Brauninger A, Wolf J, Hansmann ML, Diehl V, Kuppers R, Rajewsky K. Somatic mutations of the CD95 gene in Hodgkin and Reed-Sternberg cells. Cancer Res 2000;60:5640–5643.

[38] Shin MS, Kim HS, Kang CS, et al. Inactivating mutations of CASP10 gene in non-Hodgkin lymphomas. Blood 2002;99:4094–4099.

[39] van der Werff ten Bosch JE, Demanet C, Balduck N, Bakkus MH, De Raeve H, Desprechins B, et al. Reversion of autoimmune lymphoproliferative syndrome with an antimalarial drug: Preliminary results of a clinical cohort study and molecular observations. Br J Haematol 2002;117:176–188.

[40] Lutwick L. Infections in asplenic patients. From principles and practice of infectious diseases. 6th ed. In: Mandell, Douglas, Bennett, editors. Elsevier Churchill Livingstone; Philadelphia, PA: 2005. p 3524–3535.

[41] Heelan BT, Tormey V, Amlot P, Payne E, Mehta A, Webster AD. Effect of anti-CD20 (rituximab) on resistant thrombocytopenia in autoimmune lymphoproliferative syndrome. Br J Haematol 2002;118:1078–1081.

[42] Rao VK, Dale J, Hurley H, Dugan F, Tretler J, Straus SE. Use of mycophenolate mofetil in Children with chronic, refractory immune cytopenias associated with autoimmune lymphoproliferative syndrome (ALPS). Br J Haemat 2005; 129:534–538.

[43] Lucignani G, Paganelli G, Bomabardieri E. The use of standardized uptake values for assessing FDG uptake with PET in oncology: A clinical perspective. Nucl Med Commun 2004;25:651–656.

[44] Burton C, Ell P, Linch D. The role of PET imaging in lymphoma. Br J Haematol 2004;126:772–784.

[45] Benkerrou M, Le Deist F, de Villartay JP, Caillat-Zucman S, Rieux-Laucat F, Jabado N, et al. Correction of Fas (CD95) deficiency by haploidentical bone marrow transplantation. Eur J Immunol 1997;27:2043–2047.

[46] Sleight BJ, Prasad VS, DeLaat C, Steele P, Ballard E, Arceci RJ, et al. Correction of autoimmune lymphoproliferative syndrome by bone marrow transplantation. Bone Marrow Transplant 1998;22:375–380.

[47] Jackson CE, Fischer RE, Hsu AP, Anderson SM, Choi Y, Wang J, Dale JK, Fleisher TA, Middelton LA, Sneller MC, Lenardo MJ, Straus SE, Puck JM. Autoimmune lymphoproliferative syndrome with defective Fas: Genotype influences penetrance. Am J Hum Genet 1999;64:1002–1014.

[48] van der Burg M, de Groot R, Comans-Bitter WM, den Hollander JC, Hooijkaas H, Neijens HJ, Berger RM, Oranje AP, Langerak AW, van Dongen JJ. Autoimmune lymphoproliferative syndrome (ALPS) in a child from consanguineous parents: A dominant or recessive disease? Pediatr Res 2000;47: 336–343.

[49] Rieux-Laucat F, Deist FL, Fischer A. Autoimmune lymphoproliferative syndromes: Genetic defects of apoptosis pathways (Review). Cell Death Differ 2003;10:124–133.

[50] Cines D, Bussel JB. How I Treat: ITP. Blood Jun 7 2005; [Epub ahead of print].