

Autoimmune lymphoproliferative syndrome

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Abstract

Autoimmune lymphoproliferative syndrome (ALPS) is a disorder associated with abnormal lymphocyte apoptosis, lymphoproliferation, and autoimmunity. It is inherited as an autosomal dominant pattern with variable penetrance. The mutations in most ALPS patients are in the gene encoding the lymphocyte protein Fas. Severe lymphadenopathy and splenomegaly are common. Clinically Autoantibodies most often are directed to red blood cells, neutrophils, and platelets. Hemolytic anemia, autoimmune neutropenia, and immune thrombocytopenia purpura occur frequently. ALPS patients have lymphocytosis and a number of lymphocyte abnormalities, including the marked expansion of T lymphocytes that express alpha/beta T-cell receptors but neither CD4 nor CD8 surface markers (TCR $\alpha\beta$ + CD4- CD8-) cells. Lymphoproliferation in ALPS patients is generally benign, but they are at increased risk for the development of Hodgkin's and non-Hodgkin's lymphoma.

Key words

Apoptosis, lymphoproliferation, autoimmunity, *Fas gene*

Disease name and synonyms

Autoimmune lymphoproliferative syndrome (ALPS)
 Lymphoproliferative syndrome with autoimmunity
 Canale and Smith syndrome

Definition

The autoimmune lymphoproliferative syndrome (ALPS) is a chronic, nonmalignant lymphoproliferative disorder caused by mutations in the genes that are involved in programmed cell death (apoptosis). The impaired apoptosis causes accumulation of lymphocytes, which underlies the clinical

manifestations of lymphadenopathy, autoimmune phenomena and a markedly increased risk of malignant lymphomas.

ALPS was first described by Canale and Smith in 1967. In most cases, the disease is revealed early in life, usually before 5 years of age. This syndrome associates lymphoproliferative manifestations, such as splenomegaly and polyadenopathy with a specific immunological disorder. The latter consists of serum hypergammaglobulinemia G (hyper IgG) sometimes associated with hyper IgA, accumulations of a particular T-cell population i.e., α/β T-cell receptor (TCR)(+) CD4(-) CD8(-). Autoimmune manifestations are observed in most cases.

ALPS diagnostic criteria**Non malignant Lymphoproliferation**

Chronic splenomegaly
Polyadenopathies

Autoimmune manifestations

Hemolytic anaemia
Thrombocytopenia
Neutropenia
Other autoimmune manifestations

Biological features

Hyper-IgG (+/- hyper-IgA)
High number of double-negative $\alpha\beta$ TCR+ T cells in blood and lymphoid tissues
Autoantibodies

Family history

Lymphoproliferative syndrome
Autoimmune manifestations

Differential diagnosis

As described in the literature (van der Werff ten Bosch *et al.*, 1999), some adult patients present with a rare type T-zone lymphoma that can erroneously be considered ALPS and should be included in the differential diagnosis.

Etiology

The molecular basis of ALPS was identified in 1995 as a Fas-encoding gene mutation (Rieux-Laucat *et al.*, 1995, Fisher *et al.*, 1995.). Fas is receptor expressed on activated lymphocytes, that mediates programmed cell death. Mutations in three different genes affecting lymphocyte apoptosis have been found in ALPS patients (Jackson *et al.*, 1999; Rieux-Laucat *et al.*, 2003, Sneller *et al.*, 2003)

These mutations involve the genes encoding the Fas receptor, Fas ligand, and caspase enzymes. All 3 molecules are part of a cascade that results in apoptosis of T and B

In humans, ALPS diagnosis can be confirmed *in vitro* by functional analysis of lymphocyte sensitivity to Fas-induced apoptosis. When Fas-induced apoptosis is defective, three classifications can be defined: a complete expression defect of Fas (ALPS 0), a functional defect caused either by the expression of a mutant Fas (ALPS Ia) or by a signaling pathway defect (ALPS II). When *in vitro* Fas-induced apoptosis is normal, two other groups are defined — ALPS Ib and ALPS III. The phenotypes and genetic bases of these ALPS groups are diverse

ALPS 0

ALPS caused by complete Fas deficiency (ALPS 0) is a consequence of homozygous null mutations. To date, only 3 cases of patients with ALPS 0 have been described. As the heterozygous family members did not have the

ALPS phenotype, autosomal recessive transmission hypothesis was supported. However, another unpublished case of a family with an ALPS 0 patient does not fully support this conclusion. From this example it can be suggested that most, if not all, mutations are dominant, and that when the mutations are homozygous they lead to a more severe phenotype. This is a classical feature of dominant diseases. (Rieux-Laucat F *et al.*, *Curr Opin Immunol.* 2003)

ALPS Ia

ALPS Ia is the consequence of heterozygous *fas* mutations. More than 70 ALPS Ia patients have been described worldwide. Most of the identified mutations affect the intracellular domain (ICD); 60% are localized within the DD (A functional cellular domain called the death domain). Some ALPS Ia patients have relatives with the same apoptotic defects (and same mutations) but who are clinically asymptomatic (Jackson, *et al.* 1999; Rieux-Laucat, *et al.* 1999 Vaishnav, *et al.* 1999)

The clinical penetrance, which is therefore partial, is highest for ICD missense mutations, reaching 90%. Mutations leading to ICD truncation have a clinical penetrance of roughly 75%; the clinical penetrance drops to 30% for ECD (extracellular domain) mutations (missense and truncated mutations combined). This difference reveals the unique genotype/phenotype correlation in ALPS. No correlation is observed between mutations, the magnitude of Fas-induced apoptosis defect or the severity of the syndrome. This partial clinical penetrance strongly suggests that a second event is associated with Fas mutations to induce an overt ALPS Ia syndrome. It is likely that genetic rather than environmental factors influence ALPS expression, and these account for the variable penetrance of some of the mutations. By contrast, the discovery of a slight, but statistically significant, increase in DN T cells in healthy parents who do not carry a Fas mutation (and therefore have normal Fas-induced apoptosis) implies that the second event contributing to the development of ALPS may be independent of Fas-mediated apoptosis (Bleesing, *et al.* 2001).

ALPS Ib

A unique dominant FasL mutation has been described in a patient presenting with features of systemic lupus erythematosus together with chronic lymphoproliferation (Wu *et al.*, 1996). It was defined as ALPS Ib, although the phenotype does not fulfil criteria of classical ALPS (DN T cells and splenomegaly were absent). The clinical manifestation could represent a bias, as the FasL mutation search was performed in a cohort of patients with SLE. Additionally,

inheritance of this FasL mutation could not be proven.

ALPS II

Several patients presented with the typical clinical and immunological features of ALPS, including abnormal lymphocyte Fas-mediated apoptosis, have Fas molecule expression and sequence normal. Some data (Wang, 1999), suggested that, in addition to caspase 8, the related caspase 10 has a key role in Fas-induced apoptosis. Thus, caspase 10 appears to be involved in the apoptotic cascade of all known receptors that induce lymphocyte apoptosis. (Wang *et al.* 2001; Kischkel *et al.*, 2001). A homozygous caspase 8 mutation has been described which the defect in activation of T and B lymphocytes suggests that caspase 8 could be involved in the early steps of intracellular signaling following TCR and BCR triggering (Chun *et al.*, 2002)

ALPS III

Over than 30 patients presented with a clinical condition close to mild ALPS, associated with hypergammaglobulinemia and an excess of DN T cells in the blood have been studied. *In vitro*, activated lymphocytes from these patients exhibit normal activation of the Fas pathway and no molecular defects have been found so far. Although not demonstrated, it is plausible that, in these patients, another lymphocyte apoptotic pathway, such as Trail-R, DR3 or DR6, could be impaired.

Incidence

ALPS occurs in both sexes and has been described in patients from all over the world. It is a rare condition, which has been defined only within the past few years. Its incidence has not yet been estimated. (Jackson *et al.*, 1999; Rieux-Laucat *et al.*, 2003)

Clinical manifestations

Two forms of the disease have been identified: the severe form with neonatal or prenatal onset and a moderate one with delayed onset.

Lymphoproliferative syndrome

Lymphoproliferation is the most consistent feature. Splenomegaly can be an isolated feature with mild consequences, such as hypersplenism and mechanical discomfort, or in contrast voluminous leading to severe complications. Hepatomegaly and polyadenopathy are not always associated. When they are, as in most cases, the time to their appearance varies. Lymphnode enlargement can be, chronic, involving various areas, and so marked as to distort anatomical landmarks. In blood, hyperlymphocytosis is not constant. The lymphoproliferative syndrome

reflects the expansion of a normally rarely found T-subset that expresses $\alpha\beta$ TCR but neither CD4 nor CD8. This population is found in the peripheral blood in percentages ranging from 3% to 60%. It should be noted that the lymphoproliferative syndrome tends to shrink with time and often becomes undetectable in adults. (Jackson *et al.*, 1999; Rieux-Laucat *et al.*, 2003)

Autoimmunity

Autoimmune manifestations are the second most common characteristic in patients with ALPS. Seventy percent of the reported patients have developed clinical symptoms associated with autoantibodies. Age at onset varied considerably (in contrast to the lymphoproliferative syndrome) (Vaishnav *et al.*, 1999; Rieux-Laucat *et al.*, 1999, Strauss *et al.*, 1999) In most cases, autoantibodies are directed against hematopoietic lineages leading to anemia, thrombocytopenia and/or neutropenia. Systemic manifestations, such as vasculitis, arthritis and glomerulonephritis, are observed less often. Two cases of autoimmune hepatitis have been described in the literature. Neurological symptoms have been attributed to an autoimmune disorder. None of the patients had typical systemic lupus, anti-DNA antibodies or typical organ-associated autoimmunity, such as diabetes type I or thyroiditis. It is possible, that patients, who have not yet developed autoimmune manifestations, could do so, later in life. In some of the patients, autoimmunity tends to be severe, requiring aggressive immunosuppressive regimens.

Development of lymphoma

Although lymphoproliferation is generally benign, the incidence of eventual lymphoma is significantly increased in ALPS patients. A study of 130 patients with Fas mutations showed that the risk of Hodgkin's lymphomas is 51-fold greater in ALPS, and the risk of non-Hodgkin's lymphomas is 14-fold greater than expected compared to the experience in the general US population less than 65 years of age. (Straus *et al.* 2001). Other malignant diseases have been reported in patients with ALPS, including liver carcinoma in one patient (with hepatitis C infection) and multiple thyroid and breast adenomas together with basal cell carcinomas in another one (Drappa, *et al.* 1996), Poppema *et al.* 2004)

Diagnostic methods

Immunological findings

Hyper-IgG is a constant feature (except in 1 patient who presented with hypogammaglobulinemia), usually without a monoclonal component. It is often associated

with hyper-IgA. In contrast, serum IgM level can be low.

Blood lymphocyte phenotyping provides the main specific diagnostic criterion for ALPS : a high CD3 T-cells count, which exceeds the sum of CD4+ plus CD8+ T-cell subsets. This T-cell subset expresses the α/β TCR and it is important to distinguish it from normal α/β TCR(+) CD3(+)CD4(-)CD8(-) T-cells. This former "double-negative" T-cell population normally represents less than 1% of CD3+ T cells while ALPS patients typically have more than 3% (range : 3-60%).(Lim *et al.*, 1998)

Autoantibodies to red cells, platelets and neutrophils are frequently found. Anti-smooth muscle, anti-phospholipid, anti-nuclear antibodies and rheumatoid factors have been also detected in some patients.

Histological features

Histological examination of lymph nodes from ALPS patients shows reactive follicular hyperplasia, and paracortical expansion with immunoblasts and plasma cells. The paracortical expansion is extensive in some cases sufficiently to consider a differential diagnosis of immunoblastic lymphoma. Examination of splenic tissue from patients demonstrates lymphoid hyperplasia of the white pulp due to B cells expansion in the lymphoid follicles, while T cells accumulate in paracortical areas.

Apoptosis assay

The diagnosis is based on the Fas-induced apoptosis assay. After lymphocyte activation, apoptosis is induced for 18 hours by either an anti-Fas monoclonal antibody or soluble Fas-L. Apoptosis can be detected using different techniques (Annexin V staining, hypodiploid nuclear detection .). Activated lymphocytes from ALPS patients always exhibit defective Fas-induced apoptosis to various extents. Sequencing of the Fas-encoding gene confirms the presence of a mutation in either one or both alleles. However, in some cases, no Fas mutation is found. These latter cases define ALPS II, as illustrated by cases with Caspase 10 mutations. (Stroncek *et al.*, 2003)

Management

ALPS patients with severe autoimmune hemolytic anemia or Immune-mediated thrombocytopenia can often be successfully treated with either prednisone alone or in combination with intravenous immunoglobulins. During steroid treatment lymphadenopathy and splenomegaly may be reduced somewhat, but both return after steroid treatment is stopped. Patients with immune cytopenias refractory to splenectomy and steroid treatment have been treated with a variety of agents, including intravenous immune globulin, cyclosporine A,

vincristine, methotrexate, azathioprine, mycophenylate mofetil, or rituximab [Jackson *et al.* 1999].

Treatment of ALPS-related autoimmune disease with prednisone, interferon- α , interleukin-2 (IL-2), cyclosporine or other immunosuppressive agents is usually associated with diminishment in the size of individual lymph nodes; however, this effect is not sustained once treatment is discontinued. A small series of patients was reported to experience reductions in lymphoproliferation while treated with the antiparasitic cocktail known as Fansidar (van der Werff *et al.* 1998) Complete Fas deficiency, can be cured by allogeneic bone-marrow transplantation (Benkerrou *et al.* 1997, Sleight *et al.* 1998.)

Unresolved questions

The clinical penetrance varies from one family to another. About 70% of the carriers of heterozygous Fas mutations have clinical manifestations. Pertinently, all have lymphocytes exhibiting a defective in Fas-induced apoptosis. The different carrier phenotypes suggest that a heterozygous Fas mutation is only the first event leading to ALPS and that a second factor is necessary to develop the disease. This second factor could be either genetically determined or acquired, and remains to be defined.

The identification of defects in other receptors, ligands or signalling molecules in ALPS patients should provide a better understanding of the molecular mechanisms controlling autoimmune proliferation sometimes associated with tumor development.

Relationship between Apoptosis and Autoimmunity remains unclear

ALPS patients also have elevated levels of vitamin B12 and IL-10 but the mechanisms responsible for the increased vitamin B12 levels are not known

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