Autoimmune Lymphoproliferative Syndrome

Synonym: Canale-Smith syndrome

Autoimmune lymphoproliferative syndrome (ALPS) is characterised by immune dysregulation due to a defect in lymphocyte apoptosis. The clinical manifestations may be seen in other family members and include lymphadenopathy, splenomegaly, increased risk of lymphoma, and autoimmune disease, most often involving cells of the haematopoietic system.[1, 2]

The majority of patients with ALPS have heterozygous germline mutations in the gene for the TNF receptor-family member FAS (CD 95, Apo-1) which are inherited in an autosomal dominant fashion. Somatic FAS mutations are the second most common genetic cause of ALPS.[3]

It can present in children or adults but usually presents in early childhood.[4]

ALPS should be considered in all children with unexplained lymphadenopathy, organomegaly, or autoimmune cytopenias.[4]

Aetiology[4]

ALPS is caused by genetic defects in the genes controlling apoptosis (programmed cell death):

- The defective pathway is FAS-mediated apoptosis, which is part of the normal downregulation of the immune system involving T and B lymphocytes.
- This leads to chronic lymphoproliferation, autoimmunity and an increased risk of malignancies.
- Approximately 70% of patients have an identifiable genetic mutation.

Presentation[4]

Onset and time course

- Most patients present with lymphoproliferation (see below) in early childhood (median age approximately 1 year).
- The autoimmune manifestations usually present in early childhood; this can occur months to years after the lymphoproliferation onset.
- More rarely, it can present in adulthood.[5]
- Both lymphoproliferation and autoimmunity may improve with age.

Clinical features

Lymphoproliferation

- The most common feature of ALPS.
- Comprises lymphadenopathy, hepatomegaly or splenomegaly.

Autoimmunity

- Autoimmune destruction of blood cells is the most common feature, varying from mild and asymptomatic to severe. It affects 70% of patients and may cause:
  - Autoimmune haemolytic anaemia.
  - Immune thrombocytopenia.
  - Autoimmune neutropenia - but usually without increased risk of invasive infection, as ALPS patients can mount a neutrophil response to infection.

Other autoimmune manifestations (less common):

- Nephritis.
- Hepatitis.
- Uveitis.
- Autoimmune cerebellar syndrome.
- Colitis.
- Urticarial rashes.[6]
- Pulmonary fibrosis.
- Almost any organ can be involved.

The autoimmunity may fluctuate and can flare up with systemic illness.
Investigations

General investigations

Blood tests
These may show:

- Autoimmune-type haemolytic anaemia, thrombocytopenia, neutropenia and hypergammaglobulinaemia.
- T- and B-cell lymphocytosis.
- Positive direct Coombs’ test - direct antiglobulin test (DAT).
- Positive autoantibodies (antiplatelet and antineutrophil and antinuclear).
- Raised IgG levels, possibly also raised IgA or IgM; but some patients have hypogammaglobulinaemia.
- Raised serum B12.
- Raised interleukin-10 (IL-10).

Biopsy

- Most patients merit tissue biopsy (bone marrow or lymph nodes) initially to rule out malignancy, infections and other lymphoproliferative disorders.
- Histology of lymph nodes shows marked paracortical expansion of T cells, and other characteristic features.

Radiology

- Imaging of the liver, spleen or lymph nodes cannot accurately distinguish benign from malignant lymphoproliferation in the context of ALPS.

Diagnostic tests
The following are tests used in diagnosing ALPS and require a specialised laboratory:

- Circulating ‘double-negative T cells’ (cell phenotype CD4⁻/CD8⁻; CD3⁺, TCRαβ⁺):
  - These are markedly increased in ALPS patients (>5% increase).
  - However, false negatives can occur if there is lymphopenia.

- Defective in vitro FAS-mediated apoptosis:
  - An expensive and lengthy test only available in a few research laboratories.
  - Does not identify all subtypes of ALPS.
Diagnostic criteria

**Required criteria**
1. Chronic (> 6 months), non-malignant, non-infectious lymphadenopathy and/or splenomegaly
2. Elevated CD3+ TCRαβ+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 two separate assays.
  2. Somatic or germine pathogenic mutation in FAS, FASLG, or CASP10.
- **Secondary:**
  1. Elevated plasma sFASL levels (>200 pg/mL), plasma IL-10 levels (>20 pg/mL), serum or plasma vitamin B12 levels (>1500 ng/L) or plasma IL-18 levels >500 pg/mL.
  2. Typical immunohistological findings.
  3. Autoimmune cytopenias (haemolytic anaemia, thrombocytopenia, or neutropenia) with elevated IgG levels (polyclonal hypergammaglobulinaemia)
  4. Family history of a non-malignant/non-infectious 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.

**Differential diagnosis**
- The differential diagnosis is wide, involving other autoimmune, infectious, malignant and lymphoproliferative disorders.
- Includes Evans' syndrome (autoimmune destruction of at least two cell types) - a recent study suggests that some children diagnosed with Evans' syndrome have ALPS.

**Management**
Patient care involves haematology, immunology and genetic specialists. Some patients do not need any treatment.

In many cases, treatment for autoimmunity is required. This is usually given as short bursts of immunosuppressive medication. A suggested new treatment algorithm uses the following:
- **First-line** - prednisolone (1 mg/kg bd).
- **Second-line** - mycophenolate mofetil (moderate disease) or sirolimus (severe disease).
- **Third-line** - vincristine or methotrexate or mercaptopurine or pyrimethamine/sulfadoxine.
- **Fourth-line** - consider rituximab, splenectomy or combined immunosuppressants.

Also:
- Splenectomy should be avoided except in cases of uncontrollable hypersplenism.
- However, rituximab and splenectomy are often the treatments of choice in refractory autoimmune cytopenias in children.
- A small subset of patients responds to intravenous immunoglobulin (but most do not).
- Stem cell transplantation may have a role - currently it is reserved for those with severe disease not responding to other treatment.

Long-term follow-up is required, including surveillance for lymphoma.

**Complications**

**Increased risk of malignancy**
- Lymphoma (Hodgkin's or non-Hodgkin's) is the most common.
- Relatives who inherit the same genetic mutation may have an increased malignancy risk.
- FAS gene mutations have been reported in tumour cells from T-cell leukaemia, multiple myeloma, melanoma, non-small cell lung cancer and transitional cell carcinoma of the bladder. However, the relevance of these findings to ALPS patients is not clear.

**Infections**
- Increased risk of postsplenectomy pneumococcal sepsis, even with vaccination and antibiotic prophylaxis.
The autoimmune neutropenia itself does not usually confer an increased risk of infection, as there is usually a neutrophil response to infection. However, immunosuppressive medication (if used) may increase infection risk.

Some patients develop common variable immunodeficiency (5-10%).

**Prognosis**

- Long-term prognostic data are lacking, because this is a rare and recently identified disease. ALPS patients can live into adulthood. [8]
- Symptoms may improve as the patient ages.
- One study looking at 200 ALPS patients over the previous 15 years found the major determinants of morbidity and mortality are:[10]
  - Severity of the autoimmune disease.
  - Hypersplenism.
  - Asplenia-related sepsis.
  - Lymphoma risk (see 'Complications', above) - this requires long-term surveillance.

**Further reading & references**


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