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AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME (ALPS) : A CASE REPORT AND REVIEW OF LITTÉRATURE

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ABSTRACT

Introduction: Autoimmune Lymphoproliferative Syndrome (ALPS) is a rare genetic disorder characterized by defective apoptosis of lymphocytes, particularly via the Fas/FasL pathway. This defect leads to the accumulation of abnormal double-negative T cells ($CD3^+$ $TCR\alpha\beta^+$ $CD4^-$ $CD8^-$), chronic lymphadenopathy, splenomegaly, autoimmune cytopenias, and an increased risk of B-cell lymphoma. Most cases are due to heterozygous mutations in the FAS gene, often affecting the intracellular death domain. Somatic mutations or defects in other apoptosis-related genes such as FASL, CASP10, or FADD can also cause ALPS. **Case report** : We report an 8.5-year-old boy presenting with pallor, generalized lymphadenopathy, and splenomegaly. Laboratory and immunological work-up revealed autoimmune cytopenias and increased double-negative T cells. Genetic testing confirmed a heterozygous FAS mutation, establishing a diagnosis of ALPS-FAS. Treatment with intravenous immunoglobulins and mycophenolate mofetil led to clinical and hematologic improvement. **Discussion** : Diagnosis is based on a combination of clinical, immunological (e.g., increased DNTs, biomarkers like elevated vitamin B12, IL-10, and soluble FasL), and genetic criteria. Updated classifications distinguish ALPS subtypes depending on the genetic profile and results of functional apoptosis assays. Clinical expression is variable, and some mutation carriers may remain asymptomatic. Treatment aims to manage autoimmune manifestations, with corticosteroids as first-line therapy. In refractory cases, immunosuppressive agents such as mycophenolate mofetil or sirolimus are effective. Splenectomy is now avoided due to high infectious risk. Long-term monitoring is essential because of the increased risk of lymphoma. **Conclusion** : ALPS serves as a model disease for studying immune tolerance and lymphocyte homeostasis. Advances in molecular diagnostics have improved disease recognition, allowed for personalized therapies, and significantly enhanced patient outcomes.

INTRODUCTION

Autoimmune Lymphoproliferative Syndrome (ALPS) is a rare inherited disorder of lymphocyte homeostasis characterized by defective Fas-mediated apoptosis. The discovery of ALPS has revolutionized our understanding of programmed cell death in the immune system and revealed its crucial role in immune tolerance and lymphocyte regulation. ALPS typically manifests in early childhood and is marked by chronic lymphadenopathy, splenomegaly, multilineage cytopenias, and an increased risk of lymphoma.

We report a moroccan pediatric observation highlighting the clinical features, diagnosis, and management of ALPS-FAS.

CASE REPORT

We report the case of an 8.5-year-old boy who presented over a period of five months with cutaneous and mucosal pallor, generalized lymphadenopathy, and splenomegaly. On clinical examination, multiple firm, non-tender lymph nodes were palpable in cervical, axillary, and inguinal regions. There was notable pallor, mild splenomegaly, and no other organomegaly or significant skin lesions.

Initial laboratory investigations revealed severe anemia (Hb 5.6 g/dL), leukopenia (1,200/µL with neutrophils 500/µL, lymphocytes 500/µL), and thrombocytopenia (126,000/µL). The direct Coombs test was positive, supporting autoimmune hemolysis. And also elevated serum vitamin B12.

A bone marrow aspirate (myelogram) was performed to exclude primary marrow failure or malignant infiltration. It showed normocellular marrow with preserved trilineage hematopoiesis, adequate myeloid and erythroid precursors, and no evidence of blasts, dysplasia, or infiltration. A bone marrow trephine biopsy further

confirmed normal architecture without fibrosis, infiltration, or malignant changes.

Given the persistent lymphadenopathy, an excisional lymph node biopsy was performed. Histopathological examination revealed reactive lymphadenitis and no features of lymphoma or atypical large cells were identified.

Radiological imaging **(**Abdominal and thoracic CT scan) demonstrated multiple enlarged lymph nodes without compressive effect and splenomegaly; no hepatomegaly or other visceral abnormalities were noted.

Flow cytometric immunophenotyping of peripheral blood lymphocytes demonstrated a global lymphopenia, all absolute counts for T cells (CD3, CD4, CD8), B cells (CD19), and NK cells were below reference ranges. Immunoglobulin subclass analysis revealed elevated IgG1 and normal IgG2, IgG3, and IgG4 levels.

Genetic analysis identified a heterozygous likely pathogenic variant in the FAS gene, consistent with an autosomal dominant form of autoimmune lymphoproliferative syndrome (ALPS-FAS).

As for the Treatment, The patient required several red blood cell transfusions due to severe anemia, multiple hospitalizations and intravenous antibiotic treatments because of recurrent infections, including otitis media, pneumonia, and febrile neutropenia. When the genetic analysis identified the FAS gene, the patient received intravenous immunoglobulins (IVIG) and mycophenolate mofetil (MMF). The choice of MMF follows current recommendations for second-line immunosuppressive therapy in ALPS; sirolimus, although effective, was not available locally in Morocco. Following the initiation of treatment, the patient's hematologic parameters stabilized, transfusion requirements decreased, and his general condition improved significantly.

DISCUSSION

ALPS typically presents in early childhood, although cases with adult onset have been reported. The clinical phenotype is dominated by chronic, nonmalignant lymphoproliferation and immune dysregulation.

The lymphoproliferative Manifestations are characterized primarily by chronic Lymphadenopathy and splenomegaly which are hallmark features and are often the first signs prompting medical attention. They result from the accumulation of autoreactive lymphocytes that fail to undergo Fas-mediated apoptosis. While hepatomegaly may also occur, it is less common. Importantly, the lymphadenopathy and splenomegaly are polyclonal and nonmalignant, which distinguishes ALPS from lymphoid malignancies.

The autoimmune Manifestations are another major clinical feature of ALPS, with autoimmune cytopenias being frequent and often severe, including autoimmune hemolytic anemia (AIHA), Immune thrombocytopenia (ITP), Neutropenia, which may present concurrently in the form of Evans syndrome. Beyond hematologic involvement, a wide spectrum of other autoimmune complications has been reported, such as autoimmune hepatitis, Glomerulonephritis, Uveitis, Guillain-Barré-like syndromes (less frequent).

The immunologic Features of ALPS are distinctive and serve as key diagnostic criteria. A persistent elevation of double-negative T cells (DNTs ; $CD3^+$ $TCR\alpha\beta^+$ $CD4^-$ $CD8^-$) in peripheral blood is a diagnostic hallmark. These normally rare cells can make up more than 1.5% of total lymphocytes in ALPS patients. Hypergammaglobulinemia, particularly elevated IgG and IgA, is commonly observed and reflects ongoing immune activation. In addition, a set of characteristic biomarkers has been identified, including elevated soluble FasL**,** increased IL-10 and IL-18 **a**nd elevated serum vitamin B12, which is a highly sensitive and specific marker for ALPS-FAS.

ALPS patients, particularly those with germline FAS mutations, carry a significantly increased risk of B-cell lymphomas, often Hodgkin or non-Hodgkin types. This risk tends to increase with age and may be amplified in those who undergo splenectomy — hence why splenectomy is now avoided in most management plans.

Diagnosing ALPS requires a combination of clinical features, laboratory findings, functional assays, and genetic testing. Due to its overlap with other autoimmune and lymphoproliferative disorders, careful evaluation is necessary.

The diagnostic Criterias according to the NIH consensus workshop held in 2009 are : Required Criterias : Chronic (>6 months) non-malignant, non-infectious lymphadenopathy and/or splenomegaly, Elevated percentage or absolute number of $CD3^+$ $TCR\alpha\beta^+$ $CD4^-$ $CD8^-$ double-negative T cells (DNTs) in peripheral blood (>1.5% of total lymphocytes or >2.5% of $CD3^+$ T cells) AND at least one of the following: Impaired lymphocyte apoptosis in vitro (demonstrated by Fas-induced apoptosis assay) or Germline or somatic pathogenic mutation in a known ALPS-related gene (FAS, FASL, CASP10, FADD). As for Secondary Criterias, These support the diagnosis but are not sufficient alone: Elevated biomarkers **(**Soluble Fas ligand (sFasL)**,** IL-10**,** IL-18**,** Vitamin B12 (often >1500 pg/mL)), Autoimmune cytopenias (AIHA, ITP, neutropenia)**,** Hypergammaglobulinemia (elevated IgG and/or IgA)**,** Family history of ALPS or related features

A demonstrable apoptosis defect by functionnal assays is also useful to the diagnosis, they test the sensitivity of activated T cells to Fas-mediated cell death in vitro.

Defects in apoptosis are a hallmark of ALPS-FAS but may be normal in ALPS with somatic mutations (ALPS-sFAS) and Flow cytometry is used to assess DNT levels and immune cell phenotyping.

The Genetic testing with targeted sequencing of the FAS gene is essential in most suspected cases. Mutations may be Germline (inherited, dominant in most cases) or Somatic, restricted to hematopoietic cells (may require sorting $CD3^+$ T cells or DNTs before sequencing). If FAS is negative, sequencing of FASL**,** CASP10**,** FADD and other apoptosis pathway genes is recommended. Somatic mutations can be missed by standard Sanger sequencing; sensitive methods like deep sequencing may be needed.

The differential diagnosis of ALPS includes a range of conditions that can present with lymphadenopathy and immune dysregulation. Infectious causes such as Epstein-Barr virus (EBV) or cytomegalovirus (CMV) infections must be considered, as well as primary immunodeficiencies. Systemic autoimmune diseases, including systemic lupus erythematosus, may mimic aspects of ALPS, and lymphoid malignancies such as lymphoma or leukemia must be ruled out given overlapping clinical features.

Thus, a combination of persistent lymphoproliferation, elevated DNTs, immune dysregulation, and a demonstrable apoptosis defect or known mutation confirms the diagnosis of ALPS.

The management and treatment of ALPS centers on controlling autoimmune manifestations and preventing infectious and malignant complications. First-line therapies include corticosteroids **(**prednisone or prednisolone): Used to rapidly control severe cytopenias such as autoimmune hemolytic anemia, thrombocytopenia, or neutropenia. They provide quick immunosuppressive effects but are not suitable for long-term use due to side effects including osteoporosis, growth retardation, and increased infection risk. Intravenous immunoglobulins (IVIG) : Mainly indicated for moderate to severe autoimmune cytopenias, either alone or in combination with corticosteroids. IVIG can reduce transfusion requirements and improve overall clinical status. For steroid-refractory or relapsing cytopenias, immunosuppressants like mycophenolate mofetil Inhibits lymphocyte proliferation and reduces autoimmunity. It is effective in cases resistant to corticosteroids. Sirolimus Inhibits the mTOR pathway, which is hyperactivated in double-negative T cells (DNTs), helping normalize their expansion. Sirolimus is particularly effective in controlling cytopenias and reducing lymphadenopathy and splenomegaly, though availability may be limited in some regions. Other immunosuppressants (cyclosporine, rituximab, cytotoxic agents): are reserved for specific indications or severe refractory cases. Splenectomy, once common, is now strongly discouraged due to the high risk of overwhelming post-splenectomy infections and the potential increased risk of lymphoma.

Monitoring for lymphoma is essential, especially in adulthood. The long-term prognosis has improved significantly with earlier diagnosis, genetic counseling, and tailored immunomodulatory therapy.

CONCLUSION

ALPS is a prototypic disease of apoptosis dysregulation that offers insights into immune tolerance, autoimmunity, and lymphocyte homeostasis. Advances in molecular diagnostics have expanded our understanding of its genetic underpinnings and clinical spectrum. Future research should focus on uncovering modifier genes and optimal long-term management strategies.

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