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Cytopenias and Infection Risk in Autoimmune Lymphoproliferative Syndrome a Review of Pathophysiology and Outcomes

Maather Baqer Hussein Al-Harmooshee

Department of Bathology, College of Medicine, University of Al-Qadisiyah, Iraq.
maather.hussein@qu.edu.iq

***Corresponding Author Email:** Orass Madhi Shaheed*, **Department of Microbiology, College of Medicine, University of Al-Qadisiya, Iraq.* *orass.shaheed@qu.edu.iq,

ABSTRACT

Background: *Autoimmune lymphoproliferative syndrome (ALPS) represent apoptotic mechanism inability to preserve lymphocyte homeostasis. Allowing lymphoid mass to accumulate and autoreactive cells to persist, which frequently show up in childhood as hepatosplenomegaly, recurrent multilineage cytopenias, and chronic nonmalignant lymphadenopathy. These patients' cytopenias may be caused by splenic sequestration in addition to autoimmune complications such as immune-mediated thrombocytopenia, autoimmune hemolytic anemia, and autoimmune neutropenia. Ever since the illness was initially described in the early 1990, diagnosis and management of this syndrome' have advanced significantly. inherited genetic defect of many autoimmune lymphoproliferative syndrome patients has involved FAS 'pathway signaling proteins but there remain those patients who carry unclear genetic defects. however, autoimmune lymphoproliferative syndrome has traditionally been thought of as a major immune defect that manifests in the early childhood, its adult onset presentation is becoming more widely acknowledged, particularly in patients who have somatic FAS mutations, and those who are genetically nonspecific. Therefore, future studies may identify novel pathway or regulatory protein Significant in apoptosis and lymphocyte activation.*

Keyword: Autoimmune Lymphoproliferative Syndrome: ALPS, Cytopenias, Apoptosis.

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INTRODUCTION

Autoimmune Lymphoproliferative Syndrome is described by immune dysregulation because a defect in lymphocyte apoptosis. Clinical manifestations could be mentioned in the multiple family members and include splenomegaly, lymphadenopathy, increased risk of lymphoma and autoimmune disease, which typically involves hematopoietic cell lines manifesting as multilineage cytopenias (1). Due to accumulation of several mutations or somatic mutations, that onset may occur in adulthood without a family history (2). ALPS is characterized by the following laboratory abnormalities: expansion of T cells that express alpha or beta T cell receptor but lack both CD4 and CD8 in peripheral blood and tissue sample , "double negative T cells" DNTs (3). Increase level of "IL-10, vitamin-B12" and impaired "*FAS"* mediated apoptosis in the vitro are additional distinctive laboratory findings. The genetic flaw in the *FAS* gene has been identified in two thirds of the cases. However, it is frequently left undefined (4).

Nearly 500 patients with autoimmune lymphoproliferative syndrome have been

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identified, coming from over 300 families. However, since many patients go undiagnosed or misdiagnoses, the actual incidence and prevalence are unknown (5). The course of many of these patients has been more gradual, and it's possible that their first symptoms appeared in childhood. The diagnosis was either postponed due to the atypical clinical Sign, late referral to tertiary center or delayed onset of illness due to somatic mutations in "*FAS"*. Additionally; there have been at least seven individuals identified who carried the germline "*FAS"* mutation. were initially asymptomatic and at some point they were thought to have had a somatic genetic occurrence in the second allele encoding "*FAS"* leading to clinical sign and symptom (6).

The genetic defect in the "*FAS"* has been found in about two-thirds of ALPS patients. Currently, the most frequently found genotype in FAS is a germline mutation (7,8). Others might develop a somatic FAS mutation that is specific to DNT cells. Some patients have also been linked to abnormalities in the genes encoding caspase 10 and "*FAS* ligand" two more proteins involved in "*FAS"* mediated apoptosis pathway. The genotypes of many patients who fit diagnostic criteria for Autoimmune lymphoproliferative syndrome are unknown (8).

Pathophysiology of autoimmune Lymphoproliferative syndrome

Most patients' pathogenesis of ALPS is caused by impaired lymphocyte apoptosis, which is mediated by Fas-Fas ligand pathway (8). Thus, defect in this pathway causes lymphocytes to proliferate, it includes populations that are specific to self-antigens, which in turn causes autoimmunity (9). FAS is also believed to contribute to the inhibition of lymphocyte malignant transformation. Patients with ALPS are more likely to develop lymphoma. molecular basis of Autoimmune lymphoproliferative syndrome was elucidated in 1995 when mutations in the *FAS* gene were identified in patients with apoptosis defects. These patients with autoimmunity, lympho proliferation and raised the numbers of double negative T cells showed similar clinical phenotypes with two mouse model that caused autoimmune disease (10) the "lpr and gld" which are due to recessive mutation in genes encoding Fas "CD95, Apo-1" and Fas ligand "CD95L" respectively, leading to defective Fas mediated apoptosis. On the basis of these similarities these patients were then classified as having the autoimmune lymphoproliferative syndrome (11).

The Tumor Necrosis Factor receptor superfamily includes the cell surface receptor Fas. Activated B and T cells typically exhibit high levels of Fas expression. When its ligand (Fas ligand) engages Fas, it sets off a series of intracellular events that activate the caspase 8 and caspase 10 proteases, which in turn cause the cell to undergo apoptosis (8). Through the induction of apoptosis in excessively activated antigen driven or autoreactive cells, Fas apoptotic pathway play crucial role in the downregulation of the immune response. Due to aberrant lymphocyte survival, mutations in the Fas pathway cause autoimmunity and lymphoid hyperplasia. accumulation of lymphocytes that have not experienced normal apoptosis is the cause of the resulting lympho proliferation. The TH-2 cytokine profile of ALPS patients is believed to promote antibody production, which in turn causes the autoimmune symptoms seen in Autoimmune lymphoproliferative syndrome (12).

Clinical signs and laboratory features

The earliest presentations of Autoimmune lymphoproliferative syndrome are often that of persistent lymphadenopathy > 95% or "splenomegaly > 90% followed by autoimmunity > 70% and hepatomegaly 50% in an otherwise healthy child. Patients with germline FAS mutations typically present

earlier than somatic FAS mutations, however, both mutations have the same clinical manifestations (13). Majority of patients develop lympho proliferation at a young age without associated constitutional symptoms (14). Patients who have splenomegaly or chronic nonmalignant lymphadenopathy that lasts six months or more are eligible to meet the ALPS case definition. The lympho proliferation can wax and wane randomly before resolving in most patients after 20 year of the age (15).

The autoimmunity is the second most common clinical presentation, especially “autoimmune cytopenias” in one or more cell lineages, that are chronic and may not respond well to treatment (16). Since the lymphocyte repertoire expands during early childhood, it has been generally believed that this is most severe during this time. the autoimmune hemolytic anemia and autoimmune thrombocytopenia are more common than autoimmune neutropenia (17). The multilineage cytopenias often noticed in Autoimmune lymphoproliferative syndrome result from splenic sequestration, as well as from underlying autoimmune processes (18). The symptoms related to cytopenia are icterus, fatigue , pallor , petechiae, bleeding, and recurrent infections. It is possible to observe family history of related disorders, which are typically inherited in an autosomal dominant manner. comprehensive examination of patient's extended family for a history of lymphoma, cytopenias, splenectomies or adenopathy may offer hints for the diagnosis of Autoimmune lymphoproliferative syndrome (19).

Due to thrombocytopenia, they may also experience mucocutaneous bleeding and easy bruising. Neutropenia may be the cause of bacterial infections. Multiple autoimmune issues” of other organs, such as the eyes kidney and liver or lymphoproliferative disorders affecting numerous organ systems are also possible (20) which, given the prevalence of anti-nuclear antibodies (ANA), could be mistaken for atypical manifestations of systemic lupus erythematosus (SLE) (21).

Cytopenias brought on by autoimmune destruction or splenic sequestration are most frequent laboratory abnormalities discovered. On the other hand, monocytosis and eosinophilia might also be related findings. Rheumatoid factor (RF), anti-nuclear antigen (ANA), and positive Coomb's direct antiglobulin test are examples of autoantibodies that may be present. Additionally, hypergammaglobulinemia is commonly observed (22). Although they might not be abnormal in patients with unknown genetic mutation, “serum IL-10, soluble FAS ligand and vitamin B12” are frequently increased in Autoimmune lymphoproliferative syndrome patient with “*FAS”* mutations and can be helpful biomarker for these patient. Although; not commercially available, flowcytometry of blood for greater number of “DNTs” can be performed and is pathognomonic of Autoimmune lymphoproliferative syndrome (23).

The autoimmune lymphoproliferative syndrome identification

Children with autoimmune multilineage cytopenias, splenomegaly, and generalized adenopathy present with diagnostic challenges because their laboratory and clinical characteristics are similar to those of other childhood hematologic disorders” like “hemophagocytic lymphohistiocytosis, lymphoma, hereditary spherocytosis, Evans syndrome and Rosai-Dorfman disease". Wiskott-Aldrich syndrome and common variable immunodeficiency are two immunologic conditions linked to autoimmune phenomena that need to be differentiated from “ALPS” (24). Criteria for diagnosing Autoimmune lymphoproliferative syndrome were proposed by researchers at the National Institutes of Health in 1999. Since then,

approximately 500 Autoimmune lymphoproliferative syndrome patient have been studied globally, and after the first international Autoimmune lymphoproliferative syndrome workshop at the National Institutes of Health in 2009 substantial progress in our comprehension of disease has resulted in revisions to diagnostic criteria and classification system (25).

Currently, presence of two necessary and six additional criteria is used to diagnose ALPS. Elevated circulating TCRαβ+ DNT cells and presence of chronic lymphadenopathy or splenomegaly are required criteria. Other criteria are separated into primary and secondary categories (26). The primary additional criteria are presence of pathogenic mutation in FAS pathway genes and an aberrant lymphocyte apoptosis assay. Raised circulating biomarker, distinctive histopathology, and family history consistent with Autoimmune lymphoproliferative syndrome comprise secondary additional criteria. A patient must fulfill both of the necessary requirements as well as one of the two main extra criteria in order to receive a definitive ALPS diagnosis. If any one of the secondary additional criteria "3, 4, 5, or 6" is present along with the necessary criteria, a probable Autoimmune lymphoproliferative syndrome diagnosis can be considered (26,27).

The diagnosis of Autoimmune lymphoproliferative syndrome is made when autoimmunity symptoms are present in addition to two other criteria: enlarged lymph nodes and/or spleen, and low blood cell counts, including "low hemoglobin, platelets, and/or neutrophils". Since the spleen and lymph node are important locations for the production and storage of lymphocytes, they enlarge. Thirty to forty percent of people with ALPS also have hepatomegaly, or an enlarged liver (28). A family history of Autoimmune lymphoproliferative syndrome or another lymphoproliferative disease is taken into account when diagnosing ALPS because it is a genetic disorder (29).

Specialized laboratory tests can occasionally identify the failure of FAS-mediated cell death (apoptosis), but very few labs are prepared to perform these tests, and the results are somewhat uncertain (30). Instead, there are blood biomarkers that are strongly linked to ALPS, including elevated serum vitamin B12 levels, increased immunoglobulins, and specific proteins like soluble FAS ligand and interleukin 10 (IL-10) (31).

Frequently, there may also be autoantibodies, which are antibodies that target the person's own body, like antibodies to healthy red blood cells. Anemia low red blood cells that carry oxygen is caused by a variety of autoimmune cytopenias (low blood cell count) (32), For people with ALPS, particularly young children, thrombocytopenia low platelets that typically aid blood to clot at sites of injury and/or neutropenia low neutrophils that fight bacteria can be a severe and ongoing issue (33,48,49).

Treatment of "autoimmune lymphoproliferative syndrome" associated refractory cytopenias

Patients with immune-mediated thrombocytopenia, autoimmune hemolytic anemia, autoimmune neutropenia, and ALPS-related autoimmune cytopenias are initially treated similarly to those with sporadic immune cytopenias in other patient populations (34). The most recent, Autoimmune lymphoproliferative syndrome patient with chronic and persistent thrombocytopenia may benefit from the American Society of Hematology's (2011) updated guidelines and recommendations for treating immune thrombocytopenia. However, to assess the relative risks and benefits of any treatment, patients with chronic multilineage cytopenias must be closely monitored for a long time, (35,47).

Patients with ALPS are specifically subject to the following cautions in our practice (35,47).

1- Suppression of the immune system using corticosteroids. Because, ALPS patient frequently have chronic and refractory disease, we employ high-dose pulse therapy with intravenous methylprednisolone 5–10 mg/kg followed by low-dose oral prednisone 1-2 mg/kg maintenance therapy, which can frequently be successfully tapered over several weeks 8–12 weeks. Some patient with profoundly refractory cytopenias e.g., hemoglobin < 5 g requiring intensive care for hypoxia may need to receive intravenous methylprednisolone at doses as high as 30 mg/kg per day for 1 to 3 days. Though some of our patients have been reported to have Cushingoid body habitus, cataracts, hyperglycemia, hypertension, osteopenia, and avascular necrosis of the hip, one must be mindful of the typical short- and long-term morbidities associated with steroids. This has led us to search for ways to avoid using steroids (36).

2- Given concurrently with a pulse dose of methylprednisolone intravenous immunoglobulin G 1-2 gm/kg may help some patients with severe autoimmune hemolytic anemia by preventing “antibody mediated red cell” destruction and enabling packed red blood cell transfusion support for severe anemia. Since a large number of ALPS patients have DAT-positive status and are at risk of hemolysis, we refrain from using WinRho for isolated thrombocytopenia (37,46).

3- ALPS patients who have isolated chronic neutropenia and related infections may also benefit from subcutaneous administration of low dose 1-2 μg/kg G-CSF twice or three times per week (38). Twelve ALPS patients in our cohort and others have used standard dose rituximab 375 mg/m2 per week four times to treat refractory, chronic cytopenias in children (39). In 7 of 9 patients with ALPS and thrombocytopenia, rituximab therapy led to median response duration of 21 months range, 14-36 months. In contrast; none of the 3 children treated with rituximab for autoimmune hemolytic anemia responded. Three patients who needed replacement intravenous immunoglobulin G experienced severe and protracted hypogammaglobulinemia; one patient experienced prolonged neutropenia and one patient experienced complete lack of antibody response to polysaccharide vaccines for up to four years following rituximab infusions. Because of these toxicities, which increase the risk of infection, particularly in asplenic individuals, rituximab may need to be avoided in Autoimmune lymphoproliferative syndrome patients until all other immunosuppressive medication options have been tried (40).

4- In 2005, we first reported the use of “MMF in 13 children with ALPS administered orally “twice daily at a dose of 600 mg/m2” per dose for chronic cytopenias. According to this initial experience, MMF has prevented patients with ALPS-associated cytopenias from using chronic steroids (41,43). Patients with ALPS, particularly those with massive splenomegaly and hypersplenism, may need additional treatments because they frequently do not respond to intravenous immunoglobulin G, packed red blood cell transfusions or standard-dose short-term corticosteroid regimen (38,45). Over the previous 11 years, we have administered MMF to 61 Autoimmune lymphoproliferative syndrome patient as continuous, long-term, steroid-sparing immune suppression for

refractory and chronic cytopenias as well as other autoimmune manifestations like “glomerulonephritis, pulmonary lesions” and uveitis. Their median follow-up period is three years range: three months to eleven years and their median age is ten years (range: six months to forty-three years) (49). As indicated by the maintenance of adequate blood counts and the reduction in dosage or discontinuation of other immunosuppressive agents 56 patient responded to MMF. However, five of them later needed additional therapies as their cytopenias became more refractory, and one of them passed away due to a relapse with refractory, overwhelming AIHA following five-year period of response to MMF. In some patient MMF has enabled splenectomy to be avoided or delayed “until the very young children had aged and would be better able to handle surgical a splenia, even though 16 patients had had splenectomy prior to starting MMF. To treat severe cytopenias, MMF should only be used as a “steroid-sparing measure” and not as an initial treatment (38,41,42).

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ETHICAL CONSIDERATIONS

The study was approved by the Research Ethical Committees of Al-Qadisiyah University. Informed consent was obtained from all participants and/or their legal guardians.

CONSENT FOR PUBLICATION

Not applicable (no individual personal data included).

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CONFLICT OF INTEREST

The authors affirm that their interests are not conflicting.

AVAILABILITY OF DATA AND MATERIAL

Data generated during this study are available from the corresponding author upon reasonable request.

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