

AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME

AUTOIMUNI LIMFOPROLIFERATIVNI SINDROM

Manole Cojocaru¹, Inimioara Mihaela Cojocaru², Isabela Silosi³, Camelia Doina Vrabie⁴

¹Titu Maiorescu« University, Faculty of Medicine, Department of Physiology,
Center for Rheumatic Diseases, Bucharest, Romania

²Carol Davila« University of Medicine and Pharmacy, Clinic of Neurology,
Colentina Clinical Hospital, Bucharest, Romania

³University of Medicine and Pharmacy, Department of Immunology, Craiova, Romania

⁴Carol Davila« University of Medicine and Pharmacy, Clinical Hospital of Emergency »Sfantul Ioan«,
»Victor Babes« National Institute for Pathology and Biomedical Sciences, Bucharest, Romania

Summary: The autoimmune lymphoproliferative syndrome (ALPS) is a rare disease. ALPS is an inherited condition that affects both sexes. ALPS is not cancer, it is not infectious, and its incidence has not yet been estimated. ALPS generally does not lead to death and most individuals with ALPS are able to live normal lives. ALPS is a disorder associated with abnormal lymphocyte apoptosis, lymphoproliferation, and autoimmunity. Serologic testing is critical in the evaluation of these individuals. Lymphoproliferation in ALPS patients is generally benign, but they are at increased risk for the development of Hodgkin's and non-Hodgkin's lymphoma. It is characterized by massive lymphoadenopathy, splenomegaly, autoimmunity including episodes of immune hemolytic anemia, thrombocytopenia, and neutropenia. 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).

Keywords: immune homeostasis, abnormal lymphocyte apoptosis lymphoproliferation, autoimmune manifestations

Kratak sadržaj: Autoimuni limfoproliferativni sindrom (ALPS) jeste retko oboljenje. ALPS je nasledna bolest koja pogađa osobe oba pola. ALPS nije kancer i nije infektivno oboljenje a njegova incidenca još nije utvrđena. ALPS generalno nema smrtni ishod i većina osoba sa ALPS može da živi normalnim životom. ALPS je poremećaj povezan sa poremećenom apoptozom limfocita, limfoproliferacijom i autoimunitetom. Serološko testiranje je presudno za evaluaciju pacijenata. Limfoproliferacija je kod obolelih od ALPS uglavnom benigna, ali je kod njih povećan rizik od nastanka Hodžkinovog i neHodžkinovog limfoma. ALPS karakterišu masivna limfadenopatija, splenomegalija, autoimunitet uz epizode imunske hemolitičke anemije, trombocitopenija i neutropenija. Oboleli od ALPS imaju limfocitozu i određen broj abnormalnosti limfocita, uključujući izraženu ekspanziju T limfocita koji izražavaju alfa/beta T-ćelijske receptore, ali ne i CD4 niti CD8 površinske markere (TCR alfa/beta⁺; CD4⁻; CD8⁻ ćelije).

Ključne reči: imunska homeostaza, abnormalna apoptoza limfocita limfoproliferacija, autoimunske manifestacije

Introduction

The relationship between hematological diseases and autoimmune processes is bi-directional (1, 2). The autoimmune lymphoproliferative syndrome (ALPS) was

first described by Canale and Smith in 1967. Children can inherit ALPS from one of their parents. Individuals affected with ALPS are fully capable of fighting infection by foreign antigens. ALPS is a human disorder that affects lymphocyte programmed cell death (apoptosis), resulting in altered immune homeostasis (3, 4). ALPS stands for autoimmune lymphoproliferative (lim-pho-pro-lif-er-a-tive) syndrome. Each of these words helps describe the main features of this condition. The word autoimmune (self-immune) identifies ALPS as a disease of the immune system. Most people with ALPS

Address for correspondence:

Manole Cojocaru
Str. Thomas Masaryk No. 5 Sector 2 Postal Code 020983
Bucharest, Romania
e-mail: manole_cojocaru@yahoo.com

have episodes of autoimmune problems (5, 6). The tools used to fight germs turn against our own cells and cause problems (7). The word syndrome refers to the many common symptoms shared by ALPS patients. The word lymphoproliferative describes the unusually large numbers of white blood cells (called lymphocytes) stored in the lymph nodes and spleens of people with ALPS (8).

Lymphoproliferation is the most consistent feature and results from the gradual accumulation of lymphocytes that have not undergone normal apoptosis (9, 10).

ALPS is an immune disease resulting from non-functional or dysfunctional apoptosis of lymphocytes, and is characterized by lymphoproliferation, peripheral accumulation of double-negative $\alpha\beta$ T cells (DNTs), and disrupted lymphocyte apoptosis. ALPS is due to defects in the genes involved in programmed cell death (apoptosis). The impaired apoptosis causes the accumulation of lymphocytes, which cumulates in the clinical manifestations of lymphadenopathy, autoimmune phenomena and a markedly increased risk of malignant lymphomas (11, 12). Clinically, autoantibodies most often are directed to red blood cells, neutrophils, and platelets. Hemolytic anemia, autoimmune neutropenia, and immune thrombocytopenia purpura occur frequently (13). Glomerulonephritis is one of the characteristic features of ALPS (4).

Autoimmune manifestations are the second most common characteristic in patients with ALPS. ALPS is characterized clinically by chronic non-malignant lymphoproliferation and autoimmunity and is caused by a genetic defect in programmed cell death (apoptosis). ALPS is a disorder due to a defect of lymphocyte apoptosis, whose clinical manifestations consist of hyperplasia of lymphoid tissues and autoimmune diseases. In ALPS, unusually high numbers of white blood cells called lymphocytes accumulate in the lymph nodes, liver, and spleen, which can lead to enlargement of these organs (14).

Apoptosis is a complex biological phenomenon involving a number of distinct molecules of the death pathway, which play a central role in maintaining lymphocyte homeostasis. Apoptosis of activated lymphocytes is critical to immune homeostasis. Apoptosis can also be triggered by a variety of non-developmental stimuli in order to remove cells that represent a threat to the integrity of an organism. This includes lymphocytes that may induce an autoimmune reaction if not regulated properly. Extrinsic apoptosis in T lymphocytes is initiated by extracellular »death activators«, including Fas ligand (FasL or CD95L), a type 2 transmembrane protein released by metalloproteinases, and tumor necrosis factor (TNF). The process of apoptosis is controlled by several genes. Most people with ALPS have an altered gene that plays a major role in apoptosis. The altered gene may be passed from one gene-

ration to the next. The relationship between apoptosis and autoimmunity remains unclear. Although autoimmunity may be directed toward all the organs, the clinical phenotype is usually characterized by lymphoproliferation, lymphadenopathy, hepatosplenomegaly, autoimmune hemolytic anemia and/or thrombocytopenia (10).

Recently, alterations of different molecules participating in this death cascade have been identified as responsible for at least 4 distinct forms of ALPS. It is normal for lymphocytes to disintegrate (e.g. die) when they have done their job. In people with ALPS and in some of their affected relatives, the genetic message for the cells to die is altered, the message is not received and the cells do not die when they should. As a result, people with ALPS develop an enlarged spleen, liver and lymph glands, along with a range of other problems involving white blood cell counts and overactive immune responses (autoimmune disease). Some patients have an increased risk of developing lymphatic cancers (lymphoma) (11).

Most patients with ALPS have heterozygous mutations in the Fas gene. Genetic mutations responsible for ALPS can be passed on from generation to generation or can occur spontaneously (12).

In patients with ALPS, defective homeostasis of lymphocytes is reflected in abnormal accumulation of lymphocytes, leading to lymphadenopathy, (hepato) splenomegaly and hypersplenism, autoimmunity due to a failure to remove autoreactive lymphocytes, and inappropriate survival of lymphocytes associated with an increased occurrence of lymphoma.

Several of the laboratory findings are unique for ALPS and reflect defective Fas-mediated apoptosis and abnormal immune regulation. Much has been learned about the molecular mechanisms that underlie defective Fas-mediated apoptosis and the complex relationship between genotype, phenotype and disease penetrance. Family studies strongly suggest the contribution of one or more additional factors to the pathogenesis of ALPS. This may pertain to defective immunoregulation by an altered IL-2/IL-2 receptor system, reflected in the specific loss of CD4+/CD8+ T cells, and/or by the highly increased IL-10 levels, but other factors may equally be involved. 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.

Laboratory features include hyper-IgG (constant feature), usually without a monoclonal component, an increased number of $\alpha\beta$ +CD4- CD8- double-negative T cells and defective *in vitro* apoptosis induced by Fas receptor triggering (14).

ALPS can cause numerous problems such as: lymphocytosis, lymphopenia (primary or secondary in response to treatment), Coombs-positive hemolytic anemia, dyserythropoiesis, reticulocytosis, thrombo-

cytopenia, neutropenia, eosinophilia, expansion of other lymphocyte subsets (gamma/delta-DNT cells, CD8+/CD57+ T cells, HLA-DR+ T cells, CD5+ B cells), decreased numbers of CD4+/CD25+ T cells, decreased number of CD27+ B cells, elevated concentration of IL-10 in serum/plasma; elevated concentrations of IgG, IgA, and IgE, normal or decreased concentrations of IgM, autoantibodies (most often positive direct or indirect antiglobulin test, antiplatelet antibody, antineutrophil antibody, antiphospholipid antibody, antinuclear antibody, rheumatoid factor), (15), lymph node pathology (paracortical expansion with immunoblasts/plasma cells and DNT cells in interfollicular areas, florid follicular hyperplasia, progressive transformation of germinal centers [PTGC], increased soluble CD25, CD27, CD30, and tumor necrosis factor ligand superfamily member 6 (Fas ligand, or FasL); monoclonal gammopathy, decreased antibody responses to polysaccharide antigens, liver function abnormalities (in case of autoimmune hepatitis), proteinuria (in case of glomerulonephritis), elevated serum concentration of vitamin B₁₂. An increase in certain types of white blood cells called alpha-beta double-negative T cells which are elevated in ALPS patients (13).

Most people with ALPS have episodes of autoimmune problems (conditions in which the immune system attacks cells in the body). Not all people with ALPS will have all of its symptoms; some people have only a few. Signs of ALPS that are seen most often include the following: enlarged spleen; enlarged lymph nodes, especially in the neck and underarms; enlarged liver; skin rashes; thrombocytopenia, which can cause bruising, nose bleeds, and may pose a risk for hemorrhage (excessive bleeding); little red spots called petechiae may also show up on the skin when platelets are low; anemia, which can cause increased fatigue or pallor; neutropenia, which can create a risk for bacterial infections (12).

The diagnosis of ALPS is based on clinical findings, laboratory abnormalities including defective in vitro tumor necrosis factor receptor superfamily member 6 (Fas)-mediated apoptosis and T cells that express the alpha/beta T-cell receptor but lack both CD4 and CD8 (so-called alpha/beta double-negative T cells [α/β -DNT cells]) in peripheral blood or tissue specimens. Detected by flow cytometric immunophenotyping, these terminally differentiated in vivo-activated T cells are rare in healthy individuals and other immune-mediated (lymphoproliferative) disorders; typically they constitute less than 2% of the lymphocyte pool (2, 13).

The normal laboratory findings in ALPS have been neutrophil function, complement concentrations and function, in vitro proliferative responses of T-cells (e.g., in response to common mitogens or antigens), NK-cell and cytotoxic T-lymphocyte (CTL) function, possible decreased CTL activity in ALPS on the basis of

defective FasL, antibody responses to protein antigens (e.g., diphtheria, tetanus) (3, 13).

Autoimmunity follows lymphoproliferation in ALPS patients, with the presence of elevated serum immunoglobulin and autoantibodies. Many patients exhibit Coombs' positive hemolytic anemia and/or immune thrombocytopenia. There are several less common manifestations including anti-nuclear antibodies, autoimmune neutropenia, autoimmune hepatitis, primary biliary cirrhosis and anti-Factor VII antibodies. It is not known why this autoimmunity is directed towards the hematopoietic system, though a decline in CD4+CD25+ cells may point to a defect in regulatory cells (4, 13).

Autoimmunity, a common feature of ALPS, is often not present at the time of diagnosis or at the time of the most extensive lymphoproliferation. In many individuals with ALPS, autoantibodies can be detected years before the appearance of clinical manifestations of autoimmune disease. Autoimmunity most often involves combinations of Coombs-positive hemolytic anemia and immune thrombocytopenia (together referred to as Evans syndrome); autoimmune neutropenia is less common. The observation of primary lymphopenia, contrasting with the typical presence of lymphocytosis, suggests the possibility of autoimmune lymphopenia (as seen in other autoimmune diseases). Autoimmune cytopenias may be difficult to distinguish from the effects of concomitant hypersplenism; examination of blood smears for evidence of hemolysis and measurement of autoantibodies and the degree of reticulocytes may help in establishing the distinction (5, 13).

Continued efforts directed at both careful clinical follow-up and basic scientific investigation are needed to increase our understanding of the incidence, natural history, and pathogenesis of ALPS.

Conclusion

The autoimmune lymphoproliferative syndrome (ALPS) is an inherited disorder of the immune system that affects both children and adults. One of the causes of ALPS is defective apoptosis, or said another way, an individual has an abnormality in how well lymphocytes (immune cells) die when they are instructed to do so. ALPS is a recently recognized and rare disorder associated with inherited defects in the FAS: gene or other regulators of lymphocyte apoptosis. Nearly all ALPS patients have antibodies directed against one or more hematopoietic cell lineages. ALPS is a disorder that typically develops in early childhood but can present in adults. ALPS is a disorder associated with abnormal lymphocyte apoptosis, lymphoproliferation and autoimmunity. ALPS, caused by defective lymphocyte homeostasis, is characterized by: non-malignant lymphoproliferation (lymphadenopathy, hepatosplenomegaly with or without hypersplenism) that often

improves with age; 2) lifelong autoimmune disease, mostly directed toward blood cells; and 3) lifelong increased risk of both Hodgkin and non-Hodgkin lymphoma. ALPS can cause numerous autoimmune problems such as anemia (low count of red blood

cells), thrombocytopenia (low count of platelets), and neutropenia (low count of neutrophils, the most common type of white blood cell in humans). Immune systems in patients with ALPS are generally efficient in fighting infection.

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