

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

Section Editor: Craig M. Kessler, MD

Autoimmune Lymphoproliferative Syndrome: New Approaches to Diagnosis and Management

David T. Teachey, MD
 Assistant Professor of Pediatrics
 Divisions of Hematology and Oncology
 Blood and Marrow Transplant
 Children's Hospital of Philadelphia
 University of Pennsylvania
 School of Medicine
 Philadelphia, Pennsylvania

H&O What is autoimmune lymphoproliferative syndrome (ALPS)?

DT ALPS is a rare disorder of abnormal white blood cell (lymphocyte) survival. Patients with ALPS have a defect in the Fas apoptotic pathway, which is key to downregulating the immune system (ie, turning it off and eliminating the lymphocytes). ALPS patients have a block somewhere in that pathway.

It is a relatively rare disease, and we do not know everything about the prevalence and incidence. A few hundred cases have been reported. It was first described in the 1990s, and every year since then, the number of cases identified has been quickly increasing as more doctors are becoming aware of the condition. Many ALPS patients are often misdiagnosed with another condition, such as an idiopathic autoimmune disorder (eg, Evans syndrome), systemic lupus erythematosus, or a histiocytic disorder.

H&O What are the diagnostic criteria of ALPS?

DT The diagnostic criteria changed in 2009. The former criteria consisted of 3 mandatory characteristics: chronic nonmalignant lymphoproliferation, elevated double-negative T cells in the peripheral blood, and functional evidence of defective Fas-mediated apoptosis.

Chronic nonmalignant lymphoproliferation is defined as enlargement of the lymph nodes and/or spleen lasting longer than 6 months that is not due to cancer. Double-negative T cells are a rare T-cell subset that are CD3-positive, CD4-negative, CD8-negative, and T-cell receptor alpha/beta-positive. In healthy people, these T cells usually constitute less than 1% of the total lymphocytes. In ALPS patients, they tend to be very elevated. In other autoimmune diseases, they can be slightly elevated.

Functional evidence of defective Fas-mediated apoptosis is determined by a laboratory assay processed by only a few research centers in the United States, thus adding time to the diagnosis. There have been several concerns about the use of this assay, including questions about reliability and availability. Also, the majority of patients have an identifiable genetic mutation in an ALPS-causative gene, and this information was not used in the diagnosis until recently. Finally, there is a recently identified subtype of ALPS, called somatic-FAS ALPS, in which patients have a false negative result on the assay. The apoptosis assay involves culturing T cells from patients for weeks and exposing them to a monoclonal antibody (immunoglobulin M) against Fas. T cells from non-ALPS patients undergo apoptosis. T cells from ALPS patients do not. Patients with somatic FAS-ALPS have a mutation in *FAS* limited to the double-negative T-cell compartment. Double-negative T cells do not survive in culture, and the apoptosis assay measures Fas function in non-double-negative T cells. Accordingly, a patient with a germline mutation in *FAS* would have an abnormal apoptosis assay; however, a patient with a somatic mutation limited to the double-negative T cells would have a normal apoptosis assay.

The new diagnostic criteria were designed by my colleagues and I, as part of an international collaboration, including researchers at the National Institutes of Health. They were revised to be more inclusive. The new criteria continue to mandate chronic lymphoproliferation and elevated double-negative T cells. Now, however, the

diagnosis can be confirmed by identifying a genetic mutation in an ALPS-causative gene (*FAS*, *FASL*, caspase-10 [*CASP10*]), with the apoptosis assays, and/or by using biomarkers that are predictive of ALPS, including elevated vitamin B₁₂, interleukin-10, and soluble Fas ligand. These criteria allow almost any physician to make the diagnosis with clinical tests that are more easily obtainable. Nevertheless, a rare subset of patients who need the more specialized, research-based testing remains.

H&O When does ALPS first manifest?

DT ALPS almost always presents in childhood. The most common age of presentation is between 1 and 2 years. (There have been rare reports of the disease presenting in patients who are in their 60s.)

ALPS usually presents in 3 phases, although in some patients, these phases can occur at once. Typically, ALPS first presents with massive lymphoproliferation: big lymph nodes and a big spleen. Patients look as if they have Hodgkin lymphoma. In some patients, the lymph nodes become so swollen they can be seen across the room. Sometimes the spleen becomes so big that it fills the whole stomach, and the patient looks pregnant. The second phase of ALPS is autoimmune disease, which is the feature that most commonly requires treatment. Autoimmune disease usually manifests as destruction of blood cells. Patients present with immune thrombocytopenic purpura, autoimmune hemolytic anemia, or autoimmune neutropenia. The third clinical presentation of ALPS is cancer. Patients have an increased risk of developing lymphoma, which usually manifests when they reach their 20s or 30s. In some adult lymphoma patients, it is possible to identify childhood symptoms of ALPS.

ALPS is often an inherited condition. The increased risk of cancer can be seen in family members without clinical ALPS, but who have the genetic mutation. Lymphoproliferation, autoimmune disease, and cancer can occur sporadically throughout a family.

H&O What are the genetic mutations associated with ALPS?

DT Approximately 70–80% of patients have an identifiable mutation, the most common of which is a germline mutation in the *FAS* gene. The second most common is a somatic mutation localized to the double-negative T-cell compartment in *FAS*. A smaller subset of patients, approximately 2–3%, have a mutation in *CASP10*. There have been a couple of reports of patients having a mutation in the Fas ligand (*FASL*). The rest of patients, the other 20–30% depending on the series, have no identifiable genetic mutation.

H&O Why is genetic testing in ALPS important?

DT Genetic testing is used to confirm diagnosis and for genetic counseling. When a patient has a known *FAS* gene mutation, other family members can be monitored for malignancies, although we still do not know the actual incidence or prevalence of these secondary manifestations.

Genetic testing is also important for treatment. Ten years ago, genetic testing did not influence management; autoimmune disease in ALPS was treated like other autoimmune diseases. However, we have learned a great deal during the past decade, and things have changed. As I said, ALPS patients are most commonly treated for autoimmune disease, usually autoimmune destruction of blood cells. First-line therapies for autoimmune hematologic disease (eg, chronic idiopathic thrombocytopenic purpura, Evan's syndrome) are corticosteroids or intravenous immunoglobulin.

The second-line treatments are very different for patients with ALPS versus patients without ALPS. Commonly used second-line therapies in patients with autoimmune destruction of blood cells are splenectomy and rituximab (Rituxan, Genentech). In non-ALPS-related autoimmune disease, pneumococcal sepsis can be avoided through vaccination and treatment with penicillin. In ALPS patients who receive splenectomy, however, the risk of pneumococcal sepsis persists even if patients are vaccinated and receive antibiotics. It may be that there is a humoral immune deficiency that has yet to be identified.

Rituximab is commonly used in patients with autoimmune destruction of blood cells. It is very safe and very well tolerated; these patients stop making antibodies for a few months, but then recover. In patients with ALPS, however, rituximab is associated with a condition called *common variable immune deficiency*, in which patients never recover their ability to make antibodies. These patients may need intravenous immunoglobulin replacement for the rest of their lives.

H&O What are the treatment options for ALPS?

DT First-line treatment is steroids. Many patients with ALPS, however, have chronic autoimmune cytopenias. These patients with severe autoimmune cytopenias are in and out of the hospital. Patients cannot receive long-term treatment with steroids because of the side effects.

For second-line therapy, the 2 drugs we most often use are mycophenolate mofetil (CellCept, Genentech) and rapamycin (or sirolimus; Rapamune, Pfizer). Mycophenolate mofetil, an immunosuppressant, was the first drug studied in ALPS. Advantages of mycophenolate mofetil are that it is easy to take, it has very few side effects, it has relatively good efficacy, and it does not

require that blood levels be checked. A disadvantage with mycophenolate mofetil is that many patients have a partial response, but not a complete response. For example, a patient with a hemoglobin of 3 gm/dL might increase to 8 gm/dL on mycophenolate mofetil. Although this increase is not perfect, it is good enough to help a patient who is very sick become someone with a pretty good quality of life. The second issue with mycophenolate mofetil is that many patients relapse. Some patients will not respond at all. Treatment with mycophenolate mofetil does not affect lymphoproliferation or the double-negative T cells.

Rapamycin, a mammalian target of rapamycin (mTOR) inhibitor, has now been tested in many patients worldwide, some in the setting of a clinical trial. An advantage of rapamycin is that it often normalizes the symptoms of autoimmune disease. Most ALPS patients on rapamycin will have a complete response and achieve a normal blood count for the first time in their life since infancy. A second advantage is that rapamycin reduces lymphoproliferation; the big lymph nodes and the big spleen often melt away. Rapamycin also typically reduces the double-negative T cells to the point at which they disappear. Most patients with ALPS have positron emission tomography (PET)-avid disease that becomes PET-negative with rapamycin treatment.

An unexpected benefit we are seeing with the use of rapamycin in ALPS patients is that immune function improves. In non-ALPS patients, rapamycin causes immunosuppression—B-cell function and T-cell function decrease—and the risk of infection may increase. In ALPS patients on rapamycin, it seems as if the immune system resets to normal. (In most ALPS patients on mycophenolate mofetil, immune function decreases as would be expected on an immunosuppressant. Transition from mycophenolate mofetil to rapamycin can improve the immune function.) We have some new data suggesting that the mTOR pathway is dysregulated in ALPS. Rapamycin was initially used in ALPS because of its immunosuppressant properties, but in reality it might be a targeted medicine that is specific for ALPS, as imatinib (Gleevec, Novartis) is for chronic myeloid leukemia.

In general, the nice thing about rapamycin is that it treats the autoimmune disease and the lymphoproliferative disease, and it eliminates what is thought to be the effector cell population of ALPS, the double-negative T cells. Another hypothetical advantage is that rapamycin might decrease the risk of secondary cancers, since mTOR inhibitors are used to treat a number of lymphomas. Mycophenolate mofetil may not have this advantage, and, as it suppresses the immune system—decreasing tumor surveillance—it could possibly even increase the risk of cancer.

Despite these facts, mycophenolate mofetil is often used as frontline therapy because rapamycin is associated

with some disadvantages. During treatment with rapamycin, drug levels must be checked, especially during the beginning of therapy. Rapamycin can be associated with drug-drug interactions. In addition, approximately 10% of patients develop mouth sores. Sometimes the sores occur only during the first month of treatment.

H&O What is next in the treatment of ALPS?

DT We need to decrease our reliance on the use of steroids—not just for ALPS but for autoimmune diseases as a whole. Currently, patients with severe autoimmune cytopenia disorders might be placed on steroids at a dosage that is slowly lowered over many months. We are learning more about the chronic toxicities associated with long-term exposure to steroids, especially in young patients, including bone weakness and avascular necrosis.

One important step is to introduce second-line agents like mycophenolate mofetil and rapamycin at an earlier time. We have treated enough patients to know that rapamycin is well tolerated, has very few side effects, and seems to be very effective.

One treatment approach that is currently used less frequently is bone marrow transplant. It is always difficult to decide if an ALPS patient should undergo transplant. In the pre-rapamycin era, transplant was considered more often. The concern is that by the time the need for a bone marrow transplant is known, the patient may be too sick to receive one. In contrast, in many patients with ALPS, the autoimmune disease and lymphoproliferation improve with age. It is not ideal to transplant a patient who may have a spontaneous resolution of disease when older.

It is an exciting time to be working in ALPS because there is much international, collaborative research. We are learning more about the disease pathophysiology and management using targeted drugs.

Suggested Readings

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