Sustained remission from angioimmunoblastic T-cell lymphoma induced by alemtuzumab

Stephanie Halene, Arthur Zieske and Nancy Berliner*

SUMMARY

Background A 73-year-old woman presented with acute lower back pain, fever, chills and arthralgias. She had previously had a positive protein derivative test with a negative chest X-ray; her medical history was also remarkable for a mitral valve prolapse. Initial symptoms resolved spontaneously without therapy, but fever recurred with associated arthralgias, myalgias, diffuse and worsening lymphadenopathy, splenomegaly, and bilateral pulmonary infiltrates.

Investigations Physical examination, blood and urine cultures, MRI of the spine, echocardiogram, extensive serologies, serum and urine protein electrophoresis, immunofixation electrophoresis, bone-marrow aspiration and biopsy with flow cytometry, cytogenetics, and gene rearrangement studies, CT scan of the chest, abdomen and pelvis, whole-body PET, and lymph-node biopsy for histological examination, immunohistochemistry, and gene rearrangement studies.

Diagnosis Angioimmunoblastic T-cell lymphoma.

Management Steroids (prednisone, methylprednisolone), levofloxacin, isoniazid with pyridoxine, ciclosporin A, methotrexate, alemtuzumab, broad-spectrum antibiotics, *Pneumocystis carinii* prophylaxis, vancomycin, and clindamycin.

KEYWORDS alemtuzumab, angioimmunoblastic lymphadenopathy, angioimmunoblastic T-cell lymphoma, cytokine storm, steroids

CME

S Halene is a fellow in Hematology and Oncology, and N Berliner is Professor of Internal Medicine and Genetics and Interim Chief of Hematology, at the Yale University School of Medicine, New Haven, CT, USA. A Zieske is a hematopathologist at Baylor University Medical Center in Dallas, TX, USA.

Correspondence
*Department of Internal Medicine, Section of Hematology, Yale University School of Medicine, 333 Cedar Street, PO Box 208021, New Haven, CT 06520-8021, USA
nancy.berliner@yale.edu

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THE CASE

A 73-year-old white woman, with a medical history remarkable for a positive purified protein derivative test with a negative chest X-ray (performed in childhood) and a mitral valve prolapse, presented to the emergency department in October 2003 with sudden-onset acute lower back pain, fever, chills, and arthralgias. Her only medications were long-standing estrogen replacement therapy, calcium, and vitamin D. She was hospitalized briefly, but blood and urine cultures, MRI of the spine, and an echocardiogram were all negative. Over 2 days her symptoms resolved and she was discharged. As a result of continued low-grade fevers, she was further evaluated as an outpatient, with negative serologies for Epstein–Barr virus (EBV), cytomegalovirus (CMV), Lyme disease, HIV, hepatitis B and C, toxoplasmosis, babesiosis, and ehrlichiosis. Tests for antinuclear antibody and rheumatoid factor were also negative. A Coombs test was not performed, as there was no evidence of hemolysis.

Four weeks later, the patient deteriorated, developing a recurrent fever, arthralgias, and diffuse lymphadenopathy, necessitating rehospitalization. Laboratory test results were remarkable for a hematocrit of 32% (normal range for adult females is 38–46%), an erythrocyte sedimentation rate (ESR) of 119 mm/h (normal range for females aged >50 years is <30 mm/hr) and a serum sodium level of 129 mEq/l (normal range is 135–145 mEq/l). Lactate dehydrogenase was normal. Atypical lymphocytes were identified in peripheral blood and a serum protein electrophoresis showed marked polyclonal hypergammaglobulinemia. Flow cytometry on the peripheral blood showed no evidence of monoclonal B-cell lymphoproliferative disease; however, 8% of the lymphocytes were T cells aberrantly expressing CD10, as described in angioimmunoblastic

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T-cell lymphoma (AITL). An atypical B-cell population expressing CD43, but not CD5, was also seen. Urine protein electrophoresis and immunofixation electrophoresis showed minute amounts of free lambda and kappa light chains. Lymph-node biopsy showed partial effacement by an atypical heteromorphous infiltrate with plasmacytoid lymphocytes in a spectrum of small plasma cells to large plasmablastic forms. There were admixed small lymphocytes with occasional large immunoblastic cells and eosinophils. The large atypical lymphoid cells were positive for CD20 and CD30, but negative for CD15, epithelial membrane antigen, and anaplastic lymphoma kinase. Background small lymphocytes showed no apparent light-chain restriction. There was a large population of $CD4^+$ T cells admixed with less prominent $CD8^+$ cells. CD21 and CD10 staining revealed residual regressing follicles. CD21 immunostaining did not show prominent dendritic cell proliferation around vasculature. Flow cytometry of the lymph node again showed no evidence of clonal B cells. Clonal rearrangement of both the immunoglobulin heavy chain and the T-cell receptor-gamma gene was detected by polymerase chain reaction. *In situ* hybridization was positive for EBV. The pathology was consistent with AITL. CT scans of the chest, abdomen, and pelvis showed diffuse lymphadenopathy, predominantly in the chest. These lymph nodes showed mildly increased fluorodeoxyglucose avidity on PET.

After 4–5 days without therapy, the patient showed spontaneous improvement, and she was again discharged. She was followed as an outpatient for 3 months, at which time she developed worsening bulky lymphadenopathy, splenomegaly, fevers, myalgias, arthralgias, and bilateral pulmonary infiltrates. The lymphadenopathy and spleen were markedly fluorodeoxyglucose avid on PET. The patient was treated by her primary physician with a course of levofloxacin with no response, at which point she commenced prednisone 2 mg/kg and improved over 2–3 days. Concurrent isoniazid and pyridoxine at standard prophylactic doses (isoniazid 250 mg; pyridoxine 50 mg) were administered because of her history of tuberculosis exposure. Follow-up imaging after 3 weeks showed near resolution of the lymphadenopathy. A slow prednisone taper was started. Ciclosporin A was added at 100 mg twice daily, increasing to 150 mg twice daily, with monitoring of serum ciclosporin levels. The lowest dose of prednisone was 20 mg/day, however, as remission was short-lived, and constitutional symptoms, lymphadenopathy, pulmonary infiltrates as well as marked hypergammaglobulinemia and ESR elevation, recurred within 2–3 months. On prednisone at 2 mg/kg daily, the patient again improved, but signs and symptoms failed to resolve entirely. The patient was started on low-dose methotrexate at 10 mg weekly, with improvement, and the steroids were again slowly tapered.

Approximately 1 month into her treatment with methotrexate the patient's clinical status suddenly deteriorated, with rapid development of a sepsis-like picture with hypotension, acute respiratory distress syndrome, a non-ST-segment elevation myocardial infarction and cardiac failure. Comprehensive infectious, rheumatologic, and cardiac investigations were negative. The patient was given stress-dose steroids and treatment with alemtuzumab (Campath®, Genzyme Corporation, Cambridge, MA) was initiated (30 mg subcutaneously, three times a week for 7.5 weeks). The patient slowly improved and was transferred out of the intensive care unit. Her subsequent course was complicated by *Pseudomonas* bacteremia, and *Klebsiella* and *Proteus* urinary tract infections, which were treated with appropriate broad-spectrum antibiotics. She subsequently developed progressive pancytopenia, and bone-marrow analysis was consistent with aplastic anemia. CMV antigenemia was absent, and the aplasia was attributed to alemtuzumab, a complication that is being reported increasingly, particularly in patients treated for T-cell malignancies.[1] Aplasia improved with methylprednisolone 40 mg every 8 h, and subsequent tapering to oral daily prednisone. Over the following months the patient recovered fully, although she continued to receive prednisone at 0.5 mg/kg every other day, while receiving *Pneumocystis carinii* pneumonia prophylaxis. Toward the end of her 3-month hospitalization, the patient was found to have a corynebacterial lung abscess, which was treated with a 4-week course of vancomycin. The abscess only partially resolved, however, and she received further treatment with clindamycin as an outpatient, with complete resolution. At present, 1 year after treatment and 2 years after diagnosis, the patient is well and without evidence of disease. She continues to receive 20 mg prednisone on alternate days.

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DISCUSSION OF DIAGNOSIS

Angioimmunoblastic lymphadenopathy (AILD) was first described in the 1970s[2] as a syndrome associated with generalized lymphadenopathy, organ and bone-marrow involvement with a characteristic lymphoproliferative process, and suggestive laboratory parameters including anemia, eosinophilia, and polyclonal hypergammaglobulinemia. After the confirmation of its association with monoclonal T-cell populations, AILD was included in the Kiel classification for lymphomas as AITL[3], and is now incorporated as a distinct entity in the WHO classification of T-cell neoplasms.[4]

Patients with AITL often display characteristic laboratory abnormalities, including anemia, elevated ESR, polyclonal hypergammaglobulinemia, and high serum lactate dehydrogenase levels, many of which were present in this patient. Less frequent findings—absent in this patient—include pruritic rash, edema, pleural effusion, ascites, and arthritis.[5]

The pathologic findings in this patient were reflective of most of the findings seen in AITL, including distortion of the normal nodal architecture by small lymphocytes, histiocytes, eosinophils, plasma cells, large lymphoid cells, and atypical, small-sized to medium-sized lymphoid cells with clear cytoplasm associated with increased numbers of arborizing high endothelial venules.[1,3] In most patients, follicular dendritic cells ($CD21^+$) are conspicuous, and usually surround the high endothelial venules,[5] but this finding was absent in this patient.

T-cell receptor genes are rearranged in most cases of AITL. Immunoglobulin gene rearrangement is found in a small percentage of patients and is likely to represent expanded EBV^+ B-cell clones. A high frequency of oligoclonal, rather than monoclonal, proliferation is found. The most frequent cytogenetic abnormalities are trisomy 3, trisomy 5, and an additional X chromosome. EBV has been detected in the majority of cases, but not all. EBV positivity is predominantly detected in B cells, however, and only rarely in clonal T cells, suggesting that EBV infection is likely to be a consequence, rather than a cause, of the disease.[5,6]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of this syndrome includes a wide range of potential infections, particularly EBV, CMV, mycobacterial disease, and fungal infection; thorough evaluation with cultures and serologies is required. In addition, the presence of adenopathy and typical B SYMPTOMS raise the suspicion for lymphoma, and bone-marrow analysis with flow cytometry and gene rearrangement studies for T-cell and B-cell receptors is indicated. Finally, autoimmune disease should be considered, especially in patients with autoimmune hemolytic anemia, and appropriate serological tests should be performed. Such studies are usually negative, as in this case. Fine-needle aspiration is inadequate for diagnosis of AITL, and definitive diagnosis requires a lymph-node biopsy, together with immunohistochemistry and clonality studies.

TREATMENT AND MANAGEMENT

Most data on the clinical management and outcome of AITL are based on retrospective studies and case reports. The median survival has been reported to be less than 36 months, with overall 3-year and 5-year survivals of around 40% and 35%, respectively.[7–9] In many cases, death is related to infectious complications.

Prednisone is usually the first line of therapy, either alone or in combination with various cytotoxic agents. Second-line treatments include immunomodulatory agents such as methotrexate, ciclosporin, and interferon-α, as well as multiagent chemotherapy.[8] Durable remissions can be achieved with high-dose therapy and autologous stem-cell transplantation, but this modality has been used in only a small number of patients.[10] In addition, short-term responses have been reported in response to fludarabine and to thalidomide.[6,11] Regardless, the clinical course of the disease is aggressive, with a median survival of less than 3 years.[5,6] Alemtuzumab is an unconjugated, nonmodulating, humanized monoclonal antibody that targets the CD52 antigen. CD52 is a 21–28 kDa cell surface glycoprotein expressed on the surface of peripheral blood lymphocytes. It is highly expressed in the tonsil and the thymus, and can be detected on most monocytes and macrophages. CD52 is not expressed on other peripheral cells, such as granulocytes, platelets or erythrocytes, and it is not detectable on hematopoietic stem cells. Alemtuzumab binds to $CD52^+$ cells, where it induces cell death by a poorly defined mechanism. Evidence suggests that it might act via a combination of complement-dependent cytolysis, antibody-dependent cellular cytotoxicity, and apoptosis.[12]

GLOSSARY

B SYMPTOMS
Unspecific symptoms that raise suspicion for lymphoma; these can include drenching night sweats, unexplained weight loss (usually more than 10% of total body weight), high fever, itching, and unusual tiredness

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GLOSSARY

CYTOKINE STORM
A cascading, hyperexaggerated secondary immune response caused by extreme overproduction of inflammatory cytokines, which accumulate at the site of infection and lead to severe tissue damage

Competing interests
The authors declared they have no competing interests.

Over the past few years, a number of trials have demonstrated the clinical activity of alemtuzumab in patients with a wide range of lymphoid malignancies, and this agent has also been used in the prevention and therapy of graft-versus-host disease following allogeneic stem-cell transplantation. The extraordinarily powerful lympholytic effect of alemtuzumab leaves patients highly immunosuppressed however, and infection is the major complication of therapy.[13] Severe and prolonged myeloid hematopoietic toxicity has also been described.[14]

In this case, the patient presented with the typical clinical, laboratory, and pathologic findings of AITL. Short-lived spontaneous and medication-induced remissions are characteristic of the disease, and her course was reflective of this natural history. Two features of this case deserve comment. First, the most life-threatening manifestation of her disease was an acute presentation with a septic shock-like picture at a time when she was relapsing from treatment with methotrexate and tapering steroids. Despite clinical features suggestive of an acute episode of sepsis, no infectious agent was identified. We postulate that this picture was not septic, but rather was evidence of her rapidly progressive AITL with acute release of cytokines in a CYTOKINE STORM, leading to hypotension and diffuse capillary leak.

The second notable feature of this patient's disease was her prolonged response to alemtuzumab. Her course was punctuated by repeated relapses within 3 months of initiation of therapy with steroids, ciclosporin A, and methotrexate. Treatment with alemtuzumab was initiated in the face of life-threatening hypotension, cardiac failure, and acute respiratory distress syndrome. Despite a course marked by virtually all of the known complications of alemtuzumab, including lung abscess, sepsis, and bone-marrow aplasia, she is currently without evidence of disease 1 year after completing alemtuzumab therapy. While recognizing the potentially highly toxic complications of its use, alemtuzumab should be considered as part of the treatment armamentarium for this rare but deadly disease.

CONCLUSION

AITL is a rare lymphoproliferative disease with an aggressive natural history. Therapy with a wide variety of immunomodulatory agents and chemotherapy regimens has met with limited success, and the disease typically follows a waxing and waning course in response to most agents. This report of sustained remission from AITL, induced by alemtuzumab, suggests that this agent should be considered in the therapy of this potentially fatal disease.

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