Successful Treatment of Angioimmunoblastic Lymphadenopathy With Dysproteinemia With Fludarabine

To the Editor:

Angioimmunoblastic lymphadenopathy with dysproteinemia (AILD) is a rare lymphoproliferative disorder that occurs predominantly in older adults and is characterized by generalized lymphadenopathy, hepatosplenomegaly, fever, and a pruritic skin rash. Patients often have hypergammaglobulinemia, autoantibodies, and hemolytic anemia. The diagnosis requires a lymph node biopsy showing effacement of the normal nodal architecture with replacement by a diffuse polymorphous infiltrate, absence of germinal centers, and arborization of postcapillary venules. The prognosis of this disorder is poor, with 75% of patients dying within 2 years of presentation despite treatment. Most patients who succumb do so from infectious complications, but between 5% and 20% of patients develop B- or T-cell lymphomas or Hodgkin’s disease. Current treatment is unsatisfactory and has included single-agent and combination chemotherapy and immunosuppression with drugs such as corticosteroids and cyclosporine A, interferon-a, and danazol. We report here a case history of a patient with AILD whose disease progressed on CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy, but who has had a sustained clinical complete response to fludarabine.

The patient was a 59-year-old Hispanic man who presented with fever, a generalized pruritic rash, malaise, and neck swelling to another institution in July 1993. On the basis of inguinal lymph node and bone marrow biopsies, he was diagnosed as having AILD and treated with standard CHOP chemotherapy. Four days after treatment his symptoms began to resolve, but they recurred after 6 weeks and he was referred to the University of Chicago. On examination he appeared unwell, with a generalized pruritic and erythematous rash and fever. He had generalized lymphadenopathy, including tonsilar enlargement, but no hepatosplenomegaly. Laboratory investigations showed a hemoglobin level of 8.3 g/dL, a white blood cell count of 12,800/μL, and a platelet count of 266,000/μL. The results of a direct Coombs’ test were negative, and the results of serum protein electrophoresis were normal. A second inguinal lymph node biopsy showed an abnormal immune reaction consistent with AILD, with effacement of the usual nodal architecture, a diffuse heterogeneous infiltrate consisting of predominantly small lymphocytes, and prominent proliferation of small blood vessels. A bone marrow biopsy showed involvement by AILD. There were multiple paratrabecular and intertrabecular aggregates of an atypical infiltrate consisting of lymphocytes, plasma cells, histiocytes, immunoblasts, and eosinophils. Cytogenetic studies on bone marrow showed a normal male karyotype, and T-cell receptor gene rearrangements by Southern analysis failed to show clonality. A computed tomography (CT) scan showed extensive lymphadenopathy scattered throughout the retroperitoneum, abdomen, mediastinum, and axillae, plus bilateral pleural effusions and abdominal ascites. The results of an infection work-up were negative. The patient received a second standard dose of CHOP chemotherapy, followed by rapid resolution of his symptoms and

---

Fig 1. Treatment course.

*Given with prednisone 60 mg qd x five days
adenopathy by clinical examination. He was then maintained on oral cyclosporine A at 400 mg daily.

After 2 months, the patient again had recurrent fever, pruritic rash, and generalized lymphadenopathy. A repeat CT scan showed an increase in the size of the axillary, mediastinal, and mesenteric lymph nodes and mild splenomegaly. At this point, treatment with fludarabine at 25 mg/m²d for 5 days every 4 weeks was started and continued for a total of eight courses. The first course was administered with oral prednisone at 60 mg for 5 days. After two courses of therapy, all symptoms had resolved, and the rash and lymphadenopathy had disappeared. A CT scan after three courses showed small residual lymph nodes in the mediastinum and resolution of the previously noted splenomegaly, ascites, and pleural effusions. After six courses, a bone marrow biopsy showed some residual areas of AILD, but a repeat CT scan showed complete resolution of the previously noted lymphadenopathy. Therapy was continued for two further courses, without complications. The median white blood cell count during treatment was 4,300/µL and showed no decline over the courses. Figure 1 summarizes the clinical course of the patient. As of this writing, the patient remains in complete clinical remission, 22 months after the cessation of all therapy and 29 months after the beginning of fludarabine therapy.

To our knowledge, this is the first case report of the use of fludarabine in AILD. It shows that fludarabine can be an effective treatment of AILD and is capable of inducing remission, even in patients who relapse after multiagent chemotherapy. Furthermore, our case shows that the therapy may be well tolerated, with little effect on blood counts and with no infectious complications.

The hyperimmunoproliferative state found in AILD may be due to a disorder in T-cell function that results in the hyperstimulation of B cells. Fludarabine is a cytotoxic agent for both B- and T-cell lymphoproliferative disorders such as chronic lymphocytic leukemia, prolymphocytic leukemia, or low-grade lymphomas. The effectiveness of fludarabine may be mediated through an inhibitory effect on the abnormal T cells, via its inhibition of DNA polymerase and ribonucleotide reductase. Further studies of fludarabine in the treatment of AILD are warranted.

S. Tiong Ong
Hartmut Koeppen
Richard A. Larson
Olufumilayo I. Olopade

Section of Hematology/Oncology
The University of Chicago
The Pritzker School of Medicine
Chicago, IL

REFERENCES

Successful treatment of angioimmunoblastic lymphadenopathy with dysproteinemia with fludarabine [letter]

ST Ong, H Koeppen, RA Larson and OI Olopade