

Angioimmunoblastic Lymphadenopathy in a Patient with Allergy to Insulin:

A Case Report

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A patient with allergy to insulin experienced reactive lymphadenopathy and, later, angioimmunoblastic lymphadenopathy; all occurred within 18 months. It is suggested that insulin may be added to the list of drugs associated with the appearance of angioimmunoblastic lymphadenopathy.

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ANGIOIMMUNOBLASTIC LYMPHADENOPATHY with dysproteinemia (AILD)^{2,3,9} or immunoblastic lymphadenopathy (IBL)⁶ is characterized by fever, generalized lymphadenopathy, hepatosplenomegaly, skin rash, polyclonal gammopathy, and, frequently, by a positive Coomb's test for hemolytic anemia. The morphologic changes in the lymph nodes consist of a prominent proliferation of immunoblasts and small arborizing vessels and deposition of an amorphous material in the interstitial spaces.^{2,6} A decrease in the number of T cells and an increase in B cells have been described.⁵ The disease is believed to occur in subjects with an abnormal immune state and to represent an exaggerated immune response, frequently triggered by an allergic reaction to a drug.⁶

The present paper reports on a patient who manifested hypersensitivity to insulin, succeeded by reactive lymphadenopathy, which later progressed to AILD.

Case Report

A 67-year-old white female was admitted because of uncontrolled diabetes. She had had diabetes for 27 years and had been treated by diet, chlorpropamide, and phenformin. In 1975, she was started on a combination of insulin lente and semilente. A maculopapular rash appeared at the site of the injections soon after the beginning of treatment. Seven months later, she had a generalized maculopapular rash. After several weeks, she was given insulin Retard NPH (Leo Nordisk), but the rash reappeared. Treatment with insulin

actrapid (Novo) was begun, together with prednisone, 10 mg, and chlorpheniramine maleate, 4 mg daily.

The urinary glucose excretion exceeded 100 g/24 hours even though she received 120 units of insulin daily. Skin tests revealed immediate hypersensitivity to both bovine and porcine insulin of different types, but not to insulin actrapid (Novo) and neutral insulin (Wellcome). Hyperglycemia was finally controlled with a diet, insulin actrapid, 70 units, and prednisone, 10 mg daily. With this regimen, the patient had an occasional transient rash. Cervical and axillary lymphadenopathy and hepatosplenomegaly were noted for the first time in November 1977. Biopsy from a cervical node revealed reactive lymphadenopathy. The lymph nodes gradually receded, and the patient felt well.

In November 1978, the patient complained of malaise, night sweating, fever, and weight loss, she was rehospitalized. Examination revealed generalized lymphadenopathy with hepatosplenomegaly. The erythrocyte sedimentation rate was 80 mm after one hour (Westergren), the leukocyte count was 9900/mm³, and the differential count was normal. Hemoglobin was 11 g/100 ml, serum albumin 3.5 g/100 ml, globulin 3.2 g/100 ml. Protein electrophoresis revealed polyclonal hypergammaglobulinemia with 1.7 g/100 ml gamma globulin. IgG was 1200 mg/dl, IgM 204 mg/dl, IgA 285 mg/dl, and there was no monoclonal fraction. The C₃ concentration was 104 mg/dl; Coomb's test was negative; rheumatoid factor and cryoglobulin were not found.

Liver scan showed marked hepatosplenomegaly, but liver biopsy showed no abnormalities. Bone marrow aspirate revealed proliferation of normal plasma cells. A second lymph node biopsy (December 1978) showed loss of the normal architecture with infiltration by small lymphocytes, histiocytes, immunoblasts, and plasma cells. There was an abundance of blood vessels and an amorphous periodic acid Schiff-positive substance (Figs. 1 and 2). The pathologic picture was typical of AILD. The patient was started on 50 mg prednisone daily, and her condition improved immediately. However, three months later, while tapering off

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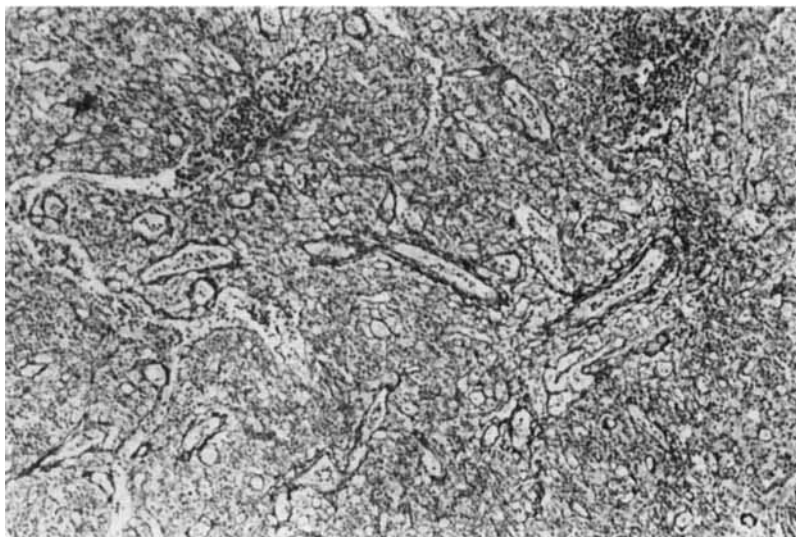


FIG. 1. Lymph node biopsy. Note abundance of small blood vessels that ramify through cellular tissue (Reticulin stain $\times 105$).

the dose, the disease flared up with fever, marked weight loss, night sweating, and generalized weakness.

A repeated lymph node biopsy revealed no change from that performed in December 1978. In April 1979, the patient was started on cyclophosphamide, and her condition improved markedly. The temperature became normal, she gained weight, and the size of the lymph nodes, the liver, and the spleen receded. The patient also received Insulin Retard N.P.H. (rare-immunogenic) and had no rash or other allergic reactions. She has remained asymptomatic until January 1980, and the hyperglycemia was well controlled. Treatment at present includes insulin, 36 units/24 hours, and prednisone 10 mg daily.

Discussion

Angioimmunoblastic lymphadenopathy and IBL are similar lymphoproliferative disorders, which resemble malignant lymphoma and are characterized

clinically by generalized lymphadenopathy, hepatosplenomegaly, fever, and rash.^{2,6} Immunologic studies in such patients have revealed an impairment in cellular immunity demonstrated by cutaneous anergy,³ a decrease in the number of circulating and lymph node T cells,⁵ and their return to normal numbers after treatment with levamisole.¹ The presence of B-cell proliferation is suggested by immunopathologic and ultrastructural studies, the high incidence of polyclonal hyperglobulinemia, and a positive Coomb's test for hemolytic anemia.¹⁰ The morphologic similarity of the lymph nodes in AILD and IBL to lymphadenopathy associated with postvaccinal lymphadenitis,³ anticonvulsant therapy,⁶ and allograft rejection⁴ suggests that chronic antigenic stimulation may be important in the pathogenesis of this disorder. Prolonged lymphoid stimulation by repetitive antigenic stimuli is known to cause lym-

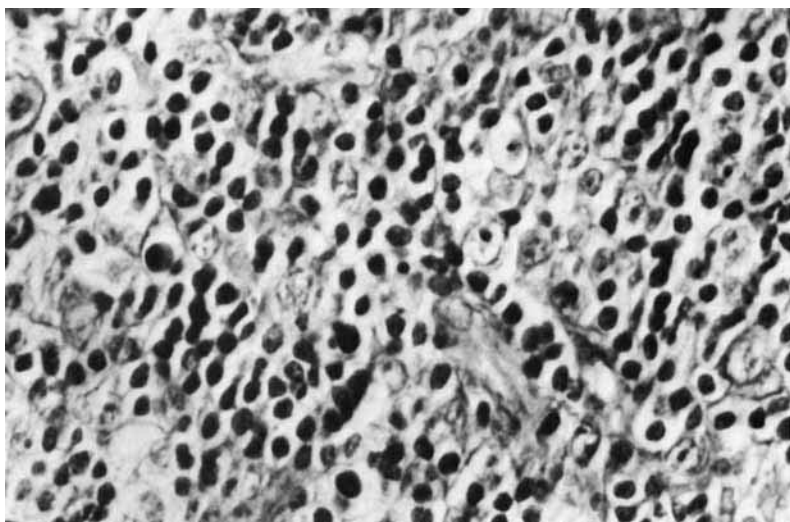


FIG. 2. Lymph node biopsy. Note large reticulum cells among numerous lymphocytes and plasma cells. Amorphous eosinophilic materials can be seen between the cells (H & E, $\times 660$).

phatic proliferation and neoplasia. In many patients, the disorder is preceded and perhaps caused by intake of drugs that allegedly serve as antigens stimulating the lymphatic system. Schultz *et al.* have demonstrated specific serum antibodies to liver extract in a patient with IBL and have suggested that antigenic stimulation by this extract, administered for treatment, played an important role in the cause of the disease.¹¹

Drugs incriminated in triggering AILD or IBL include penicillin,^{3,6} sulphonamide derivatives,^{3,6} gentamycin,⁷ erythromycin,⁷ diphenylhydantoin,^{3,6} griseofulvin,^{3,6} primidone,⁸ aspirin,³ halothane,³ barbituates,⁷ liver extract,¹¹ and methyldopa.¹² Insulin has so far not been reported as a possible etiologic agent.

Our patient had insulin hypersensitivity manifested by recurrent skin rash. This was followed by the appearance of reactive lymphadenopathy and AILD, all occurring within about 18 months. We suggest that insulin may be added to the list of drugs associated with the appearance of AILD.

REFERENCES

1. Bensa JD, Faure J, Martin H, Sotto JJ, Schaerer R. Levamisole in angioimmunoblastic lymphadenopathy. *Lancet* 1976; 1:1081.
2. Frizzera G, Moran EM, Rappaport H. Angioimmunoblastic lymphadenopathy with dysproteinemia. *Lancet* 1974; 1:1070-1073.
3. Frizzera G, Moran EM, Rappaport H. Angioimmunoblastic lymphadenopathy. Diagnosis and clinical course. *Am J Med* 1975; 59:803-818.
4. Graham RC. Pathogenesis of vascular proliferation in angioimmunoblastic lymphadenopathy with dysproteinemia. *Lancet* 1974; 2:666.
5. Kosmidis PA, Axelrod AR, Palacas C, Stahl M. Angioimmunoblastic lymphadenopathy: a T-cell deficiency. *Cancer* 1978; 42:447-452.
6. Lukes RJ, Tindle BH. Immunoblastic lymphadenopathy. A hyperimmune entity resembling Hodgkin's disease. *N Engl J Med* 1975; 292:1-8.
7. Matz LR, Papadimitriou JM, Carroll JR, *et al.* Angioimmunoblastic lymphadenopathy with dysproteinemia. *Cancer* 1977; 40:2152-2160.
8. Moore B, Harrison E, Wieland L. Angioimmunoblastic lymphadenopathy. *Mayo Clin Proc* 1976; 51:273-280.
9. Nathwani BN, Rappaport H, Moran EM, Gerassimos AP, Kim H. Malignant lymphoma arising in angioimmunoblastic lymphadenopathy. *Cancer* 1978; 41:578-606.
10. Neiman RS, Dervan P, Haudenschild C, Jaffe R. Angioimmunoblastic lymphadenopathy: an ultrastructural and immunologic study with review of the literature. *Cancer* 1978; 41:507-518.
11. Schultz DR, Yunis AA. Immunoblastic lymphadenopathy with mixed cryoglobulinemia: a detailed case report. *N Engl J Med* 1975; 292:9-12.
12. Weisenburger DD. Immunoblastic lymphadenopathy associated with methyldopa therapy: a case report. *Cancer* 1978; 42:2322-2327.