

Angioimmunoblastic Lymphadenopathy in a Patient Taking Diphenylhydantoin

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ABSTRACT

The premise that chronic antigenic stimulation may be involved in lymphoproliferative disorders was considered in a patient with angioimmunoblastic lymphadenopathy who had received diphenylhydantoin (DPH) for seizure. This patient had clinical features overlapping with systemic lupus erythematosus (SLE) and serum antibody directed against DPH. It was proposed that the syndrome was caused by chronic antigenic stimulation with DPH.

Angioimmunoblastic lymphadenopathy (AIBL) is a non-neoplastic disease of lymphocyte proliferation characterized by a histopathology and clinical course distinct from that of Hodgkin's disease, with which it has been confused. Lukes and Tindle described the nodal architecture as a "triad of plasmacytoid and plasma cells, proliferation of small arborizing vessels and deposition of amorphous eosinophilic interstitial material."⁸ Clinical manifestation includes fever, skin rash, lymphadenopathy, polyclonal hypergammaglobulinemia, and often Coombs-positive hemolytic anemia.²⁻⁹

Recently, attention has been drawn to the similarities between AIBL, systemic lupus erythematosus (SLE) and dilantin induced lymphadenopathy.^{9,10,12} Herein

is described a case of AIBL with clinical and serologic features characteristic of SLE. It is interesting that this patient had antinuclear antibody (ANA) which could be adsorbed with the sodium diphenylhydantoin (DPH) which she had been taking. It was proposed by the present authors that the AIBL syndrome of this patient was caused by chronic antigenic stimulation with dilantin and that the pathogenic pathways are most likely those proposed by Gleichmann et al.³

Case History

A 70-year-old white female sought medical care at Broadsay Methodist Hospital with a history of progressive weakness and marked fatigue. Two weeks prior to admission, she developed a maculopapular rash on her face. Craniotomy had been previously performed for removal of a meningioma, and she had

been maintained on dilantin for seizures which developed after surgery.

On physical examination, the patient appeared chronically ill with a temperature of 39°C. She had generalized lymphadenopathy, with firm, movable and tender nodes ranging from 1 to 3 cm in diameter.

The hemoglobin was 9.2 g per dl, the hematocrit 28 percent, and the white count 5,300 per mm,³ with 60 percent segmented neutrophils, 11 percent band forms, eight percent lymphocytes, 20 percent monocytes, and one percent eosinophil. Platelets appeared adequate in number. The sedimentation rate was 60 mm per hr.

Direct and indirect Coombs tests were negative. The ANA titer was 1:320 with a speckled pattern. The lupus erythematosus (LE) preps were positive times three. Serum levels of lactic dehydrogenase, aspartate aminotransferase, and alkaline phosphatase were all elevated. Serum protein electrophoresis was interpreted as showing a polyclonal gammopathy. Immunoglobulin levels determined by immunodiffusion showed: IgG 4,050 mg per dl (normal; 700 to 1700), IgM 110 mg per dl (normal; 70 to 210), IgA 1,125 mg per dl (normal; 70 to 350).

An axillary lymph node biopsy showed obliteration of the normal architecture. Prominent proliferation of arborizing vessels and occasional deposits of amorphous interstitial material were found (figure 1). The predominant cell population consisted of large, immature cells with prominent nucleoli, as well as plasma cells, lymphocytes and histiocytes (figure 2). A biopsy of the posterior iliac crest showed bone marrow involvement with a lesion similar to that described in the lymph node. The patient developed pleural effusions and was referred to University of Chicago Medical Center. Following the diagnosis of AIBL, dilantin was discontinued. She received six cycles of chemotherapy with nitrogen mustard, vincristine, procarbazine and prednisone

(M.O.P.P.), and the lymphadenopathy resolved. Her ANA titer was normal when she was seen four months after admission.

Special Studies

Antinuclear antibody was determined with a commercial kit.*

For the absorption studies, one volume of DPH powder was mixed with two volumes of the patient's serum. The mixture was incubated for 24 hours at 25°C, centrifuged, and the supernatant assayed for ANA. The sediment was washed up to six times and used for antibody elution. The washed sediment was mixed with two volumes of saline and incubated at 56°C for 10 minutes with frequent agitation. After centrifugation, the eluate was tested for ANA. A serum positive for ANA to the same titer as that of the patient was used as control. Ampicillin powder was a negative control.

Results and Discussion

In table I are summarized the results of the special studies. It was demonstrated

* ElectroNucleonic Laboratories, Inc., Bethesda, MD 20014.

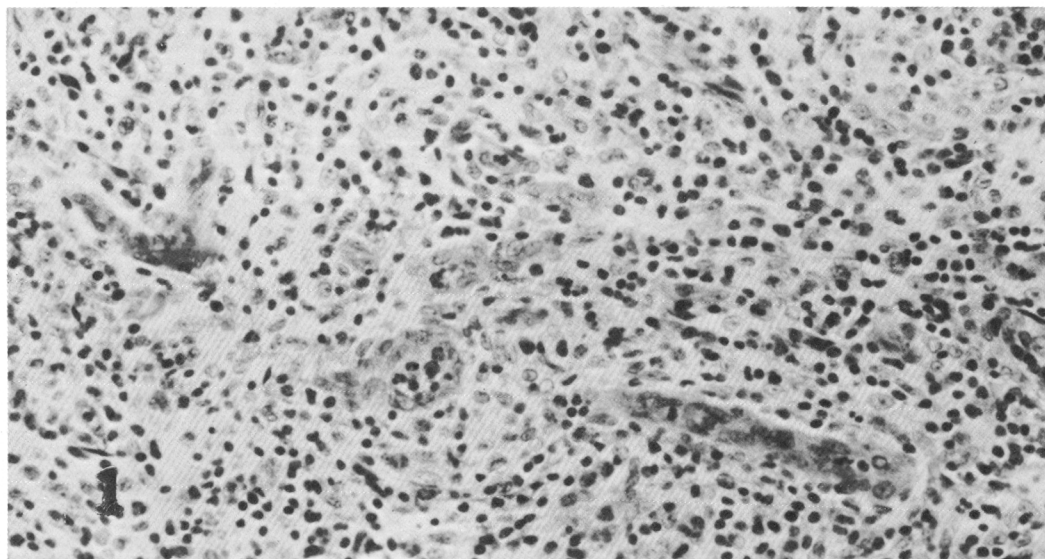


FIGURE 1. Proliferation of small arborizing vessels. (Hematoxylin-Eosin stain $\times 100$).

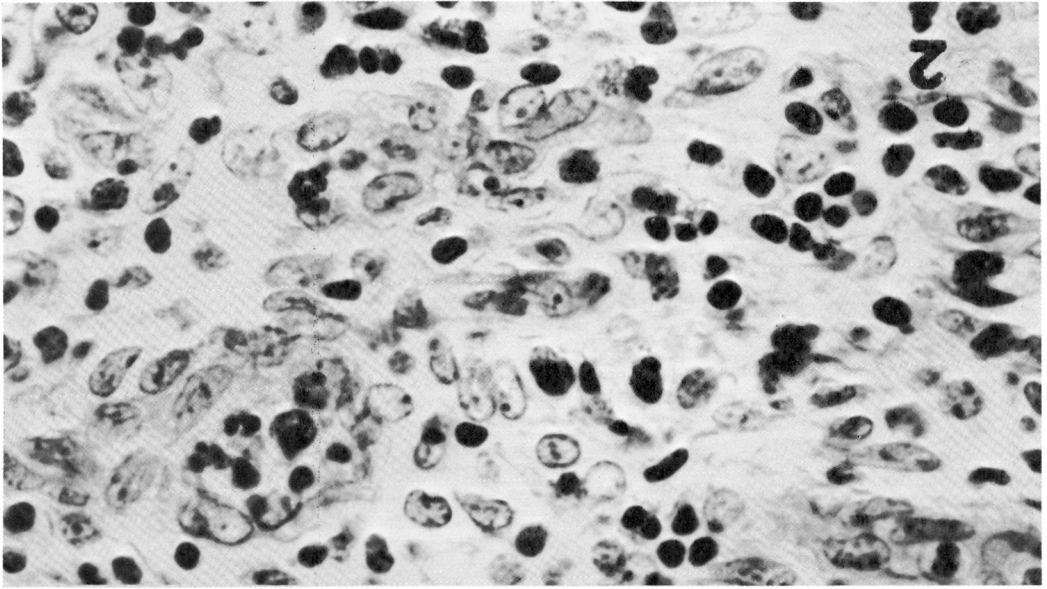


FIGURE 2. Lymph node biopsy showing immunoblasts, plasma cells and lymphocytes. (Hematoxylin-Eosin stain $\times 400$).

that this patient had an ANA titer of 1:320 which could be efficiently adsorbed by diphenylhydantoin and then eluted by heat. The antibody in the control serum was not adsorbed by diphenylhydantoin, and the patient's antibody could not be adsorbed with ampicillin powder. This indicated that the antibody present in the patient's serum cross reacted with diphenylhydantoin; it also is specific for nucleic acid.

Two unique features of this case are the simultaneous presence of LE cells and of serum ANA reactive to diphenylhydantoin. The latter finding suggests strongly that chronic antigenic stimulation by this drug could play an important role in pathogenesis.

In AIBL, ANA and anti-DNA have been reported in only two patients, one of whom had anti-double-stranded DNA.¹¹ Cullen et al² reviewed over 200 cases of AIBL in the literature and none had positive LE cells. Pierce et al¹⁰ described a patient like ours diagnosed as AIBL with features of SLE. Neiman et al⁹ also observed similarities between AIBL and SLE.

Lukes and Tindle⁸ observed strikingly similar morphology between AIBL and adenopathy associated with anticonvulsant therapy. In our case, a lymph node analysis made at AFIP was interpreted as DPH-induced lymphadenopathy, although a consultant at University of Chicago described it as a classical case of AIBL. It is apparent that distinction between AIBL and DPH-induced lymphadenopathy may be difficult. Our case also represents a morphological overlap between AIBL and DPH-induced adenopathy. In addition, the vascular changes noted in the involved lymph nodes in AIBL are similar to those described in such immunologic reactions as

TABLE I

Antinuclear Antibody Titer of Patient and Control Sera Before and After Absorption With Diphenylhydantoin

	Before Absorption	After Absorption	Elution of Sediment
Patient Serum	1:320	0	1:160
Control Serum	1:320	1:320	0

allograft rejection⁴ and post-vaccination lymphadenopathy.⁵

Gleichmann et al³ postulated possible common pathogenetic pathways for AIBL, SLE, and DPH-induced lymphadenopathy. Their concept is based on two different lines of experimental evidence. (1) In animal graft-versus-host models, immunoblastic lymphadenopathy, angiogenesis, dermatitis, and generalized autoantibody formation were induced by reactions of parental B-cells toward genetically incompatible major histocompatibility complex structures. (2) A similar syndrome can be induced by T-cell reactions toward genetically incompatible major histocompatibility complex structures or toward major self-histocompatibility complex structures that were rendered "foreign" in an as yet undefined manner by virus or chemicals.

It is possible that DPH can alter the major histocompatibility complex, making it foreign to T and/or B cells. Benign as well as malignant lymphomas are known to develop in patients under DPH therapy, and some have been diagnosed as immunoblastic sarcoma.^{1,6,7} Diphenylhydantoin was among the list of therapeutic agents implicated as possible triggers to AIBL.⁸ It differs from the known lymphocyte mitogen, such as concanavalin A, and bacterial lipopolysaccharide, however, since it failed to behave as a non-specific mitogen when added to cultured human lymphocytes. Diphenylhydantoin may behave as a hapten. Gleichmann et al³ postulated that DPH attached to the membranes of lymphoreticular cells and rendered them immunogenic for autologous T lymphocytes. This could result in graft-versus-host reaction of T cells to other lymphoid cells and the subsequent

development of diseases such as lymphocyte proliferation, angiogenesis, auto-antibody formation and dermatitis.

References

1. ANTHONY, J. J.: Malignant lymphoma associated with hydantoin drugs. *Arch. Neurol.* 22:450-454, 1970.
2. CULLEN, M. H., STANSFELD, A. G., OLIVER, R. T., ET AL: Angioimmunoblastic lymphadenopathy: Report of ten cases and review of the literature. *Quart. J. Med.* 189:151-177, 1979.
3. GLEICHMANN, E., ELVEN, F. V., GLEICHMANN, H.: Immunoblastic lymphadenopathy, systemic lupus erythematosus and related disorders. *Amer. J. Clin. Pathol.* 72:708-723, 1979.
4. GRAHAM, R. C.: Pathogenesis of vascular proliferation in angioimmunoblastic lymphadenopathy with dysproteinemia. *Lancet* 2:666, 1974.
5. HARTSOCK, R. J.: Postvaccinal lymphadenitis. Hyperplasia of lymphoid tissue that simulates malignant lymphoma. *Cancer* 21:632-649, 1968.
6. IASHIMA, C. K.: Lymphoma and anticonvulsive therapy. *J. Amer. Med. Assoc.* 228:286-287, 1974.
7. LI, F. P., WILLARD, D. R., GOODMAN, R., ET AL: Malignant lymphoma after diphenylhydantoin (Dilantin) treatment. *Cancer* 36:1359-1362, 1975.
8. LUKES, R. J. and TINDLE, B. H.: Immunoblastic lymphadenopathy; a hyperimmune entity resembling Hodgkin's disease. *New Eng. J. Med.* 292:1-7, 1975.
9. NEIMAN, R. S., DERVAN, P., HAUDENSCHILD, C., ET AL: Angioimmunoblastic lymphadenopathy: An ultrastructural and immunologic study with review of the literature. *Cancer* 41:507-518, 1978.
10. PIERCE, D. A., STERN, R., JAFFE, R., ET AL: Immunoblastic sarcoma with features of Sjogren's syndrome and systemic lupus erythematosus in a patient with immunoblastic lymphadenopathy. *Arthritis Rheum.* 22:911-916, 1979.
11. PRUNZANSKI, W., SUTTON, D. M. C., PANTALONY, D.: Angioimmunoblastic lymphadenopathy: an immunologic study. *Clin. Immunol. Immunopathol.* 6:62-75, 1976.
12. SCHECHTER, S. L. and ROSENBLUM, D.: Immunoblastic lymphadenopathy and hydroxychlorquine. *Arthritis Rheum.* 23:256-257, 1980.