# IMMUNOBLASTIC LYMPHADENOPATHY ASSOCIATED WITH METHYLDOPA THERAPY

## *A Case Report*

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**The case of a 71-year-old woman who developed generalized weakness, lymphadenopathy, and a skin rash during methyldopa therapy is described. The prompt disappearance of symptoms following the discontinuation of the drug implicates it in the initial triggering of the abnormal lymphoid proliferation. Shortly thereafter, florid immunoblastic lymphadenopathy developed, and the patient subsequently responded to corticosteroid therapy. The frequent occurrence of immunoblastic lymphadenopathy during or shortly after the administration of various therapeutic medications is emphasized. The nature of the disorder and its differential diagnosis are discussed.**

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A VARIETY OF nonneoplastic lymphadenopathies may clinically and pathologically stimulate malignant lymphoma. In recent years a hyperimmune lymphoproliferative disorder termed "immunoblastic lymphadenopathy" has been described.[7,11] The disorder occurs chiefly in older patients and is clinically characterized by constitutional symptoms, generalized lymphadenopathy, hepatosplenomegaly, skin rash, polyclonal gammopathy, and frequently a Coombs-test-postive hemolytic anemia. Morphologically, the entity is characterized by a nonneoplastic appearing mixed cellular proliferation with a prominent immunoblastic component, proliferation of small arborizing blood vessels, and deposition of variable amounts of amorphous eosinophilic interstitial material.[7,11] The disorder has frequently been confused histologically with malignant lymphoma, most commonly Hodgkin's disease.

Approximately one-third of the patients reported in the two largest series[7,11] developed the disorder during or shortly after the administration of various medications, most commonly antibiotics, and clinically were thought to have drug hypersensitivity reactions. The following report describes a similar case which occurred during therapy with methyldopa, an association that has not been previously reported.

### CASE REPORT

A 71-year-old Caucasian female developed painful, tender, bilateral cervical and supraclavicular lymphadenopathy in January 1977, accompanied by generalized weakness and fatigue, and a diffuse erythematous skin rash, with urticaria and pruritis. The patient had been taking methyldopa (Aldomet)* 250 mg daily for five years for mild hypertension. Laboratory data included a hemoglobin of 10.8 g/dl, leucocyte count 2,400/mm$^3$ with 57% neutrophils and 43% lymphocytes, erythrocyte sedimentation rate 83 mm/h, and a negative direct Coombs test. The patient was thought to have a drug reaction and methyldopa was discontinued, resulting in dramatic diminution of the lymphadenopathy and disappearance of the skin rash over the next few days.

The patient presented six weeks later with progressive weakness, dyspnea on exertion, and a five pound weight loss. Enlarged, bilateral axillary and inguinal lymph nodes and prominent hepatosplenomegaly were noted. The hemoglobin was 5.4 g/dl, and the leucocyte count 1800/cc mm with 68% lymphocytes, 28% segmented neutrophils, and 4% bands. The platelet count was 177,000/cc mm, reticulocyte count 1.4%, and erythrocyte sedimentation rate 128 mm/h. An axillary lymph node biopsy specimen was interpreted as atypical hyperplasia, and a bone marrow biopsy specimen showed focal lymphoid infiltrates. Because of a clinical diagnosis of malignant lymphoma, and

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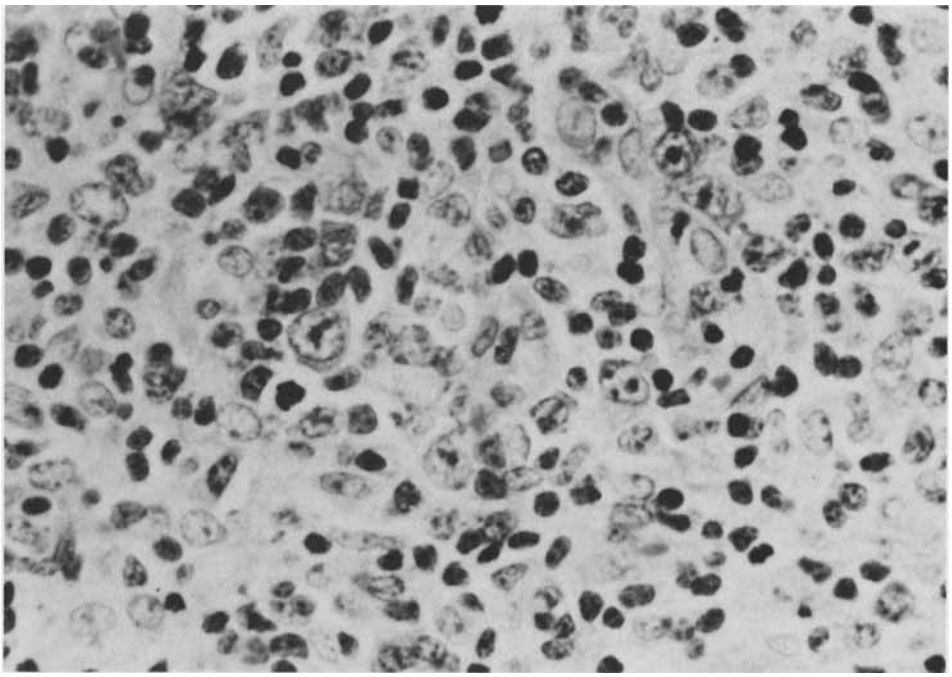

FIG. 1. Lymph node showing a mixed cellular infiltrate with a prominent component of immunoblasts (H & E, ×160).

difficulty cross matching the patient's blood, she was referred to the University of Iowa Hospitals for further evaluation. The physical examination was unchanged. Review of the lymph node and bone marrow biopsy specimens led to a diagnosis of immunoblastic lymphadenopathy. Additional laboratory data included a serum iron of 57 μg/dl and a total binding capacity of 232 μg/dl. Lactate dehydrogenase and haptoglobin levels were normal, and direct and indirect Coombs tests were negative. The total protein was 6.2 g/dl with a gamma globulin fraction of 1.3 g/dl. Immunoelectrophoresis showed a mild diffuse increase in IgM. No Bence-Jones protein was present. Quantitative serum immunoglobulins included an IgG of 1070 mg/dl (normal 800–1800 mg), IgA 90 mg/dl (normal 90–450 mg), and IgM 350 mg/dl (normal 70–200 mg). Low titer cold agglutinins were present. Complement evaluation included a $C_3'$ of 39 mg/dl (normal 55–140 mg), $C_4'$ 16 (normal 20–50 mg), and a total hemolytic complement of 72 units (normal 72–168 U). Monospot and anti-nuclear antibody tests were negative. Skin testing with mumps, Dermatophyton, and purified protein derivative (PPD) antigens was negative, but the patient responded to dinitrochlorobenzene (DNCB) sensitization. Viral and fungal titers were nondiagnostic.

The patient was treated with moderate doses of corticosteroids. Gradual resolution of the patient's symptoms, lymphadenopathy, hepatosplenomegaly, anemia, and leucopenia occurred over the next two months. The corticosteroids were gradually tapered.

The patient relapsed in January 1978 while taking small doses of corticosteroids. She complained of increasing fatigue, weight loss, night sweats, and a pruritic erythematous papular skin rash. Generalized tender lymphadenopathy and splenomegaly were present. The hemoglobin was 7.9 g/dl, leucocyte count 1600/mm$^3$ with severe neutropenia, and the platelet count was 247,000/mm$^3$. Direct and indirect Coombs testing was positive and the warm reacting antibody had specificity for the small c Rh antigen. The lactate dehydrogenase was 616 IU/liter, plasma free hemoglobin 10.5 mg/dl, serum haptoglobin 9 mg/dl, and the reticulocyte count was 1.2%. Quantitative serum immunoglobulins included an IgG of 680 mg/dl, IgA 44 mg/dl, and IgM 70 mg/dl. The $C_3'$ measured 74 mg/dl and the $C_4'$ was 54 mg/dl. Axillary lymph node and bone marrow biopsy specimens showed immunoblastic lymphadenopathy. The patient was treated with high doses of corticosteroids but showed no response. A splenectomy was performed. The spleen weighed 1010 g and showed diffuse infiltration with immunoblastic lymphadenopathy and prominent erythrophagocytosis. The anemia and leucopenia improved only transiently. Enlarging adenopathy developed and a cervical lymph node biopsy specimen showed immunoblastic lymphadenopathy with focal small clusters of immunoblasts suggestive of malignant transformation. A bone marrow biopsy specimen showed

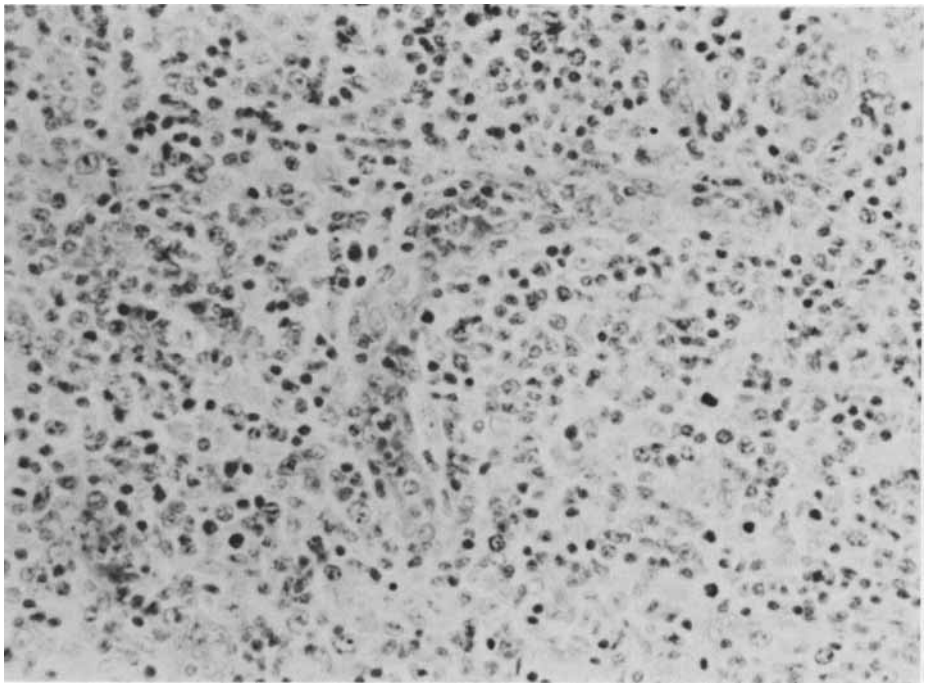

FIG. 2. Lymph node showing a mixed infiltrate, numerous immunoblasts, and prominent arborizing small blood vessels (H & E, ×80).

extensive infiltrates with a "depleted" appearance and hypoplasia of the normal marrow elements. The patient was treated with moderate doses of cyclophosphamide and developed severe pancytopenia. She died suddenly shortly thereafter, presumably of sepsis. An autopsy was not performed.

## Light Microscopy

Sections of the axillary lymph node showed diffuse effacement of the normal architecture by a mixed cellular proliferation consisting of a prominent component of immunoblasts accompanied by plasma cells, plasmacytoid lymphocytes, and lymphocytes of variable differentiation (Figs. 1, 2). Marked pyroninophilia was present. Histiocytes were present in small numbers, either singly or in small clusters (Fig. 3). A marked proliferation of finely arborizing small blood vessels was present diffusely, with hyperplasia of the endothelium (Fig. 2). Amorphous eosinophilic interstitial material was present focally in small amounts. The capsule was focally obliterated with infiltration of the perinodal adipose tissue. The peripheral sinuses were focally compressed. A few residual germinal centers of the epithelioid type were present. No Reed-Sternberg cells, necrosis, fibrosis, vasculitis, or granulomas were present.

The bone marrow smears were markedly hypocellular. A trephine biopsy specimen showed focal, large, paratrabecular and central, mixed cellular infiltrates similar to those present in the lymph node (Fig. 4). Reticulin fibers were markedly increased in these areas. Microvascular proliferation was not prominent. The normal cellular elements of the marrow were markedly decreased in number.

TABLE 1. Drugs Incriminated in Triggering Immunoblastic Lymphadenopathy

| Drugs | References |
|---|---|
| Penicillin | 7, 11, 12 |
| Sulfa | 7, 11 |
| Griseofulvin | 7 |
| Gentamycin | 12 |
| Erythromycin | 12 |
| Diphenylhydantoin | 7, 11, 14 |
| Primidone | 14 |
| Aspirin | 7 |
| Halothane | 7 |
| Barbiturate, aluminum hydroxide-xylocaine mixture | 12 |
| Liver extract | 18 |
| Methyldopa | Present case |

## DISCUSSION

The onset of immunoblastic lymphadenopathy during or following the administration of various therapeutic medications occurs in a significant number of cases. Drugs incrimi-

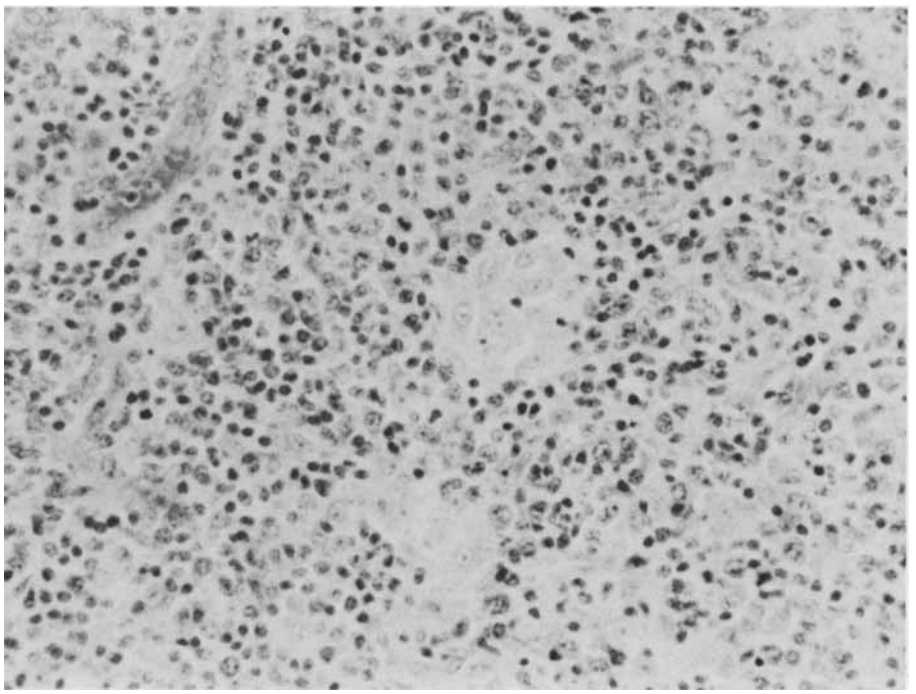

FIG. 3. Lymph node showing a mixed infiltrate with small clusters of histiocytes (H & E, ×80).

nated to date in triggering the reaction are included on Table 1. We are not aware of a previous report of immunoblastic lymphadenopathy associated with methyldopa therapy. The dramatic onset of a generalized skin rash and lymphadenopathy in our patient is typical of those cases of immunoblastic lymphadenopathy associated with drugs.[7,11] The prompt disappearance of these symptoms following the discontinuation of methyldopa therapy implicates the drug in the initial triggering of the abnormal lymphoid proliferation. The recurrence of florid immunoblastic lymphadenopathy, and the subsequent response to corticosteroid therapy in our patient are not unusual,[7] although the occurrence of a spontaneous remission cannot be excluded.

Immunoblastic lymphadenopathy is thought to represent a non-neoplastic hyperimmune proliferation of the B-lymphocyte system,[11] perhaps related to an impairment of T-cell regulatory functions.[7] A B-cell origin for the proliferating cells is supported by immunohistologic and ultrastructural studies.[12,15,20] Profound depression of circulating T-cells,[2,15] lymph node T-cells,[15] and cellular immunity as demonstrated by skin testing,[2,7,21] also support the above hypothesis. Bensa *et al.*[2] have demonstrated the return of peripheral T and B cell levels and cellular immunity to normal, after the treatment of one patient with Levamisol, a stimulant of the T-cell system. The morphologic similarity of lymph nodes from patients with immunoblastic lymphadenopathy to antigenically stimulated lymph nodes,[9] and the presence of polyclonal hypergammaglobulinemia suggest that chronic antigenic stimulation of the lymphoid system is occurring. Schultz *et al.*[18] have demonstrated the presence of specific serum antibodies to the proposed triggering agent in one patient. The recent description of hypocomplementemia and vasculitis in some patients with immunoblastic lymphadenopathy[21] suggests that circulating immune complexes may be present and responsible for some of the clinical manifestations of the disorder. Matz *et al.*[12] have shown impairment of the humoral response to specific exogenous antigens in the presence of increased serum immunoglobulin levels in one patient. In some cases the abnormal lymphoid proliferation appears to have been triggered by a drug, as in the case reported here. In most cases a specific stimulus has not been identified. Even after discontinuation of a known triggering agent, the lymphoid proliferation generally continues, often with

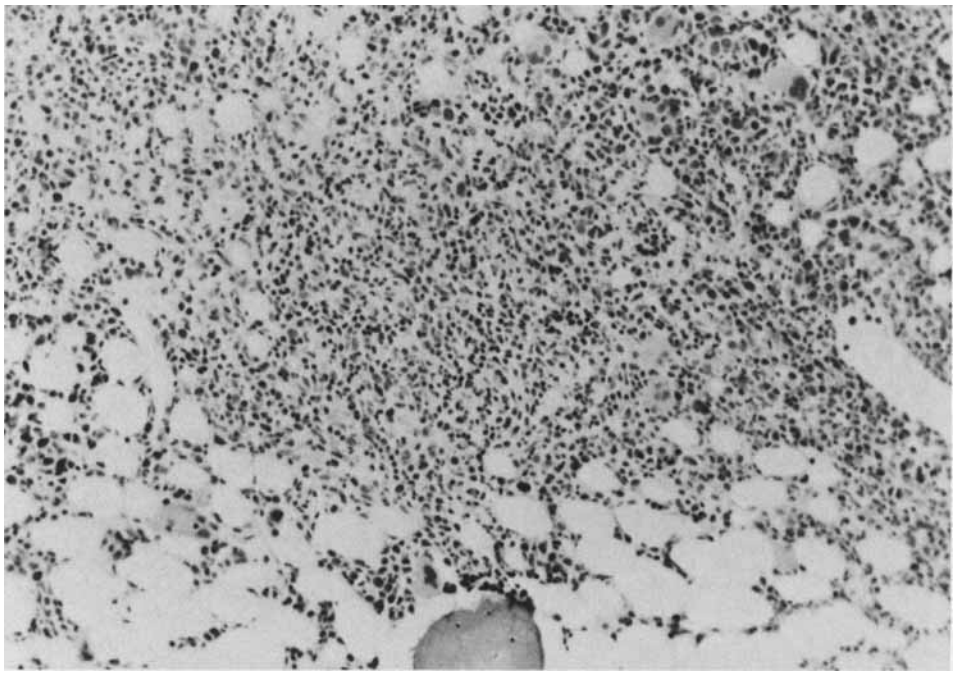

FIG. 4. Bone marrow showing a focal mixed cellular infiltrate (H & E, ×40).

a fatal outcome. Immunoblastic lymphadenopathy may well represent an abnormal systemic hyperimmune response to known[18] or unknown antigens,[21] occurring in individuals with altered cellular immunity. A possible defect in the lymphocyte system, with loss of the physiological suppressive T-cell influence on the B lymphocyte, may result in abnormal proliferation and hyperactivity of the B-cell system.

The nonspecific morphology of the lymph nodes in immunoblastic lymphadenopathy exemplifies the difficulties in pathologically defining where an immune proliferative process stands in the spectrum of lesions from "atypical" reactive to frankly malignant. Postvaccinial and herpetic lymphadenitis,[9] infectious mononucleosis,[17,19] and diphenylhydantoin induced lymphadenopathy[16] may closely resemble immunoblastic lymphadenopathy. Lymphadenopathy mimicking Hodgkin's disease has been reported in patients with systemic lupus erythematosis.[13] The pseudolymphoma of Sjögrens syndrome[1] is also morphologically similar to immunoblastic lymphadenopathy, and is thought to occupy a middle position in the spectrum of lymphoproliferation ranging from benign to malignant.

Lukes and Tindle[11] have described the morphologic evolution of three of their patients with immunoblastic lymphadenopathy into immunoblastic sarcoma, a neoplasm which they have also observed to develop in patients with other chronic abnormal immune disorders such as systemic lupus erythematosis, rheumatoid arthritis, Sjögren's syndrome, alpha-heavy-chain disease, and drug related immunosuppression. Immunoblastic lymphadenopathy has also been reported to evolve into immunoblastic leukemia,[5] lymphoplasmacytic lymphoma associated with gamma-heavy-chain disease,[6] and Hodgkin's disease.[22] The transformation of diphenylhydantoin lymphadenopathy,[4,8] and the pseudolymphoma of Sjögren's syndrome[1] into a malignant lymphoma characterized by large transformed lymphocytes, presumably immunoblasts, is also known to occur. The morphologic overlap between immunoblastic lymphadenopathy, immunoblastic sarcoma, and lesions classified as Lennert's lymphoma[3] can also pose a difficult diagnostic problem to the pathologist. The transformation of Lennert's lymphoma to immunoblastic sarcoma has been recently reported.[10]

Little is known about the natural history of untreated immunoblastic lymphadenopathy

because in the past patients were usually treated for a neoplastic process. In at least some cases the disorder appears to represent a premalignant state. Many deaths have been related to chemotherapy induced pancytopenia and infection.[7,11] A good clinical response has been reported in a limited number of patients treated with supportive therapy and corticosteroids,[7,21] and it would seem reasonable on this basis to reserve combination chemotherapy for those patients developing overt malignancy or aggressive disease unresponsive to conservative management.

It appears that our understanding of the lymphadenopathies associated with abnormal immunologic reactions is still incomplete. Further investigation, both morphologic and cytochemical, as well as clinical and immunologic, is needed to classify these disorders properly and treat them appropriately.

## REFERENCES


1. Anderson, L. G., and Talal, N.: The spectrum of benign to malignant lymphoproliferation in Sjögren's syndrome. *Clin. Exp. Immunol.* 10:199–221, 1972.
2. Bensa, J. C., Faure, J., Martin, H., Sotto, J. J., and Schaerer, R.: Levamisole in angioimmunoblastic lymphadenopathy. *Lancet* 1:1081, 1976.
3. Case records of the Massachusetts General Hospital.: *N. Engl. J. Med.* 297:206–211, 1977.
4. Clinicopathologic conference. Lymphoma as drug reaction occurring during hydantoin therapy for epilepsy.: *Am. J. Med.* 32:286–297, 1962.
5. Fischer, R. I., Jaffe, E. S., Braylan, R. C., Anderson, J. C., and Tan, H. K.: Immunoblastic lymphadenopathy. Evolution into a malignant lymphoma with plasmacytoid features. *Am. J. Med.* 61:553–559, 1976.
6. Frizzera, G., Long, J. C., and Berard, C. W.: Evolution of angio-immunoblastic lymphadenopathy. *N. Engl. J. Med.* 297:59–60, 1977.
7. Frizzera, G., Moran, E. M., and Rappaport, H.: Angio-immunoblastic lymphadenopathy. Diagnosis and clinical course. *Am. J. Med.* 59:803–818, 1975.
8. Gams, R. A., Neal, J. A., and Conrad, F. G.: Hydantoin-induced pseudo-pseudolymphoma. *Ann. Intern. Med.* 69:557–568, 1969.
9. Hartsock, R. J.: Postvaccinial lymphadenitis. Hyperplasia of lymphoid tissue that simulates malignant lymphomas. *Cancer* 21:632–649, 1968.
10. Klein, M. A., Jaffe, R., and Neiman, R. S.: "Lennert's lymphoma" with transformation to malignant lymphoma, histiocytic type (immunoblastic sarcoma). *Am. J. Clin. Pathol.* 68:601–605, 1977.
11. Lukes, R. J., and Tindle, B. H.: Immunoblastic lymphadenopathy. A hyperimmune entity resembling Hodgkin's disease. *N. Engl. J. Med.* 292:1–8, 1975.
12. Matz, L. R., Papadimitriou, J. M., Carroll, J. R., Barr, A. L., Dawkins, R. L., Jackson, J. M., Herrmann, R. P., and Armstrong, B. K.: Angioimmunoblastic lymphadenopathy with dysproteinemia. *Cancer* 40:2152–2160, 1977.
13. Miller, D. G.: The association of immune disease and malignant lymphoma. *Ann. Intern. Med.* 66:507–521, 1967.
14. Moore, B. S., Harrison, L. G., and Wieland, L. H.: Angioimmunoblastic lymphadenopathy. *Mayo Clin. Proc.* 51:273–280, 1976.
15. Palutke, M., Khilanani, P., and Weise, R.: Immunologic and electron microscopic characteristics of immunoblastic lymphadenopathy. *Am. J. Clin. Pathol.* 65:929–941, 1976.
16. Saltzstein, S. L., and Ackerman, L. V.: Lymphadenopathy induced by anticonvulsant drugs mimicking clinically and pathologically malignant lymphoma. *Cancer* 12:164–182, 1959.
17. Salvador, A. H., Harrison, E. G., and Kyle, R. A.: Lymphadenopathy due to infectious mononucleosis: Its confusion with malignant lymphoma. *Cancer* 27:1029–1040, 1971.
18. Schultz, D. R., and Yunis, A. A.: Immunoblastic lymphadenopathy with mixed cryoglobulinemia. A detailed case study. *N. Engl. J. Med.* 292:8–12, 1975.
19. Tindle, B. H., Parker, J. W., and Lukes, R. L.: "Reed-Sternberg cells" in infectious mononucleosis? *Am. J. Clin. Pathol.* 58:607–617, 1972.
20. Valdes, A. J., and Blair, O. M.: Angioimmunoblastic lymphadenopathy with dysproteinemia. Immunohistologic and ultrastructural studies. *Am. J. Clin. Pathol.* 66:551–559, 1976.
21. Weisenburger, D., Armitage, J., and Dick, F.: Immunoblastic lymphadenopathy with pulmonary infiltrates, hypocomplementemia, and vasculitis: A hyperimmune syndrome. *Am. J. Med.* 63:849–854, 1977.
22. Yataganas, X., Papadimitriou, C., Pangalis, G., Loukopoulos, D., Fessas, P., and Papacharalampous, N.: Angio-immunoblastic lymphadenopathy terminating as Hodgkin's disease. *Cancer* 39:2183–2189, 1977.