Immunoblastic Lymphadenopathy with Pulmonary Infiltrates, Hypocomplementemia and Vasculitis

A Hyperimmune Syndrome

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A detailed description of the clinical and morphologic characteristics of four patients with immunoblastic lymphadenopathy, pulmonary infiltrates, hypocomplementemia and vasculitis is presented. Noteworthy in the patients described here is the clinical similarity to patients with collagen-vascular diseases and systemic drug reactions. The frequent occurrence of pulmonary symptoms, bilateral interstitial infiltrates and pleural effusions is emphasized. The morphology suggests stimulation of the immune system by antigenic agents, and the low complement levels and the presence of vasculitis suggest that circulating immune complexes may be present. Immunoblastic lymphadenopathy may represent a syndrome in which the adenopathy is but a nonspecific part of a systemic hyperimmune response to unknown antigens. The clinical course of the patients reviewed suggests that supportive treatment and corticosteroids constitute the safest therapeutic approach.

Immunoblastic lymphadenopathy is a recently described lymphoma-like entity characterized by a diffuse proliferation of immunoblasts, plasma cells, lymphocytes and small blood vessels in lymph nodes, and systemic involvement of multiple organs. The disease occurs chiefly in older patients and is clinically characterized by constitutional symptoms, generalized lymphadenopathy, hepatosplenomegaly, skin rash, polyclonal gammopathy and, frequently, a Coombs' test-positive hemolytic anemia [1,2]. Immunoblastic lymphadenopathy is clinically similar to the collagen-vascular diseases and to systemic drug reactions in many respects. Iseman and associates [3] have recently emphasized the occurrence of symptomatic lung disease in a patient with immunoblastic lymphadenopathy. Hypocomplementemia and vasculitis, however, were not described in their patient or in the two largest series [1,2]. We present four patients with immunoblastic lymphadenopathy who, in the course of their disease, manifested prominent pulmonary symptoms accompanied by hypocomplementemia and vasculitis.

MATERIALS AND METHODS

This study is based on a review of the clinical features and pathologic findings of four patients evaluated at the University of Iowa Medical Center within the past four years. In each case the lymph node morphology met the criteria proposed by Lukes and Tindle [1]. The cases were also selected on the basis of a correlation of previously described characteristic clinical and laboratory findings in immunoblastic lymphadenopathy [1,2] with the appropriate morphologic characteristics. In all cases, tissue for diagnosis consisted of lymph nodes obtained by biopsy in the pretreatment phase of the disease.

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Formalin-fixed paraffin sections 4 μ thick were stained with hematoxylin and eosin, periodic acid-Schiff, methyl-green-pyronin and for reticulin. Additional material, including peripheral blood smears, bone marrow smears and sections, pleural fluid cytology, and skin and muscle biopsy specimens, were reviewed. Autopsies were performed on two patients, and the histologic sections and autopsy protocols were reviewed.

CLINICAL OBSERVATIONS

Patient Characteristics. The four patients consist of two men, aged 42 and 72 years, and two women, aged 60 and 67 years. Three patients were farmers and one a pottery worker. No patient had a prior history of autoimmune disease. Three patients had no history of allergies or medication intake prior to the onset of illness. One patient (Case 1, Table 1) had a childhood history of asthma and ragweed allergy. This patient had built a new hog confinement facility a few months before the onset of his illness, and related fever and wheezing for 1 to 2 hours after working in this facility. This patient had also received penicillin frequently in the past for various minor complaints, the most recent exposure two months prior to the onset of illness. Another patient related a rash after several exposures to insecticides, prior to the onset of illness.

Signs and Symptoms. All patients presented with fever, malaise, anorexia, hepatosplenomegaly and generalized lymphadenopathy; the nodes measured 1 to 4 cm. Three patients complained of myalgias, two of arthralgias, two of sweats, two of weight loss and two of sore throat. One patient (Case 4) presented with a diffuse maculopapular rash, urticaria and angioneurotic edema, and another had a transient maculopapular rash following chemotherapy. One patient had generalized petechiae.

In all four patients bilateral interstitial pulmonary infiltrates and pleural effusions developed sometime during their course. All complained of shortness of breath and dry cough, three of dyspnea on exertion, two of dyspnea at rest, two of wheezing and one of pleuritic chest pain. Pulmonary symptoms were a prominent part of the symptom complex in three of four patients and among the presenting symptoms in two patients.

Laboratory Examination. All patients presented with anemia, the hematocrit value ranging from 25 to 35 per cent. Two patients had Coombs' test-positive hemolytic anemia. One patient presented with a leukocytosis of 26,400/mm^3 and 30 per cent eosinophils, whereas another had 14 per cent eosinophils. Three patients had mild rouleaux and circulating abnormal plasmacytoid lymphocytes, ranging from 5 to 20 per cent, on peripheral blood smear. Ten per cent of the cells from one patient (Case 3) were plasmacytoid immunoblasts, characterized by large, eccentric, immature nuclei, 1 to 3 prominent nucleoli and abundant, deeply basophilic cytoplasm with occasional vacuoles. A peripheral blood smear was not available on one patient. One patient (Case 1) presented with thrombocytopenia, the platelet count being 95,000/mm^3 and subsequently decreasing to 7,000/mm^3. A platelet survival study using autologous chromium 51 (^{51}Cr) labelled platelets showed marked splenic sequestration. The serologic test for syphilis (VDRL), antinuclear antigen and latex fixation tests were negative in all patients, and one patient tested had a negative heterophil test.

All four patients had a polyclonal hypergammaglobulinemia (Table I). Two patients had significant increases in immunoglobulins G (IgG), M (IgM) and A (IgA). One patient had an elevated IgG level only. One patient had an elevated IgM level only, cryoglobulins, a prolonged serum viscosity and the hyperviscosity syndrome. One patient (Case 3) had mild Bence Jones proteinuria. Two patients (Cases 2 and 3) had elevated cold agglutinin levels and positive Coombs' tests. Two patients had significantly depressed serum complement levels, including the third (C3) and fourth (C4) components of complement and total complement. Another patient had a depressed total complement level, whereas the other patient (Case 2) had repeatedly normal total complement levels. C3 and C4 were not determined in these two patients. The inhibitor to the esterolytic subunit of the first component of complement (C1 esterase inhibitor) was present in the patient with angioneurotic edema. A farmer's lung battery performed on the farmer with hog confinement exposure yielded negative results. Three patients had no response to skin testing with a variety of antigens including purified protein derivative, mumps, Dermatophyton, histoplasmin and dinitrochlorobenzene (DNCB). One patient reacted to ragweed antigen.

TABLE I Immunologic Parameters

Findings	Case 1	Case 2	Case 3	Case 4
IgG (mg/100 ml	1,860 (800–1,800)	2,010 (853–1,463)	4,740 (800–1,800)	1,690 (800–1,800)
IgM (mg/100 ml)	186 (60–250)	1,040 (72–126)	600 (60–250)	840 (70–280)
IgA (mg/100 ml)	74 (90–450)	310 (139–261)	540 (95–450)	287 (90–450)
Serum viscosity	. . .	3 min, 4 sec (<3 min)	. . .	7 min, 35 sec (<3 min)
C3 (mg/100 ml)	35 (80–140)	. . .	. . .	31 (80–140)
C4 (mg/100 ml)	0 (20–50)	. . .	. . .	4 (20–50)
Total complement (U)	<50 (72–168)	84 (72–168)	<50 (72–168)	50 (72–168)
Vasculitis	+	+	Not biopsied	+
Skin tests	Ragweed pos.; PPD neg.	Dermatophyton, PPD, mumps, DNCB neg.	Dermatophyton, PPD neg.	Dermatophyton, PPD, histoplasmin neg.

NOTE: Parentheses indicate normal values. PPD = purified protein derivative; DNCB = dinitrochlorobenzene.

Roentgenographic Findings. The chest roentgenograms revealed bilateral, reticular, interstitial infiltrates (Figure 1) in all four patients during their course, usually in a basilar distribution. All patients had significant, bilateral pleural effusions, and two had mediastinal and hilar adenopathy. Diffuse hepatomegaly or splenomegaly was present on liver-spleen scans in all patients.

Course of Disease. One patient (Case 1), the farmer initially exposed to the hog confinement facility, presented with significant pulmonary symptoms, lymphadenopathy and thrombocytopenia. A diagnosis of immunoblastic lymphadenopathy, based on findings in the lymph nodes, was made. A muscle biopsy specimen showed vasculitis, and subsequently a right foot drop developed. Motor neuron conduction was absent in the right leg, consistent with denervation, and subsequent testing showed increased polyphasic motor units, compatible with reinervation. This patient was treated initially with large doses of corticosteroids; there was a prompt amelioration of pulmonary symptoms and lymphadenopathy, a gradual increase in the platelet count to normal and no further progression of the vasculitis. The corticosteroid dosage has been tapered without a recurrence of symptoms, but serum complement levels remain depressed, suggesting persistent low grade disease.

The second patient (Case 2) presented with lymphadenopathy, pulmonary infiltrates, prominent eosinophilia and hemolytic anemia. A diagnosis of atypical lymphoid hyperplasia, based on the findings in the lymph nodes, was made (later reclassified as immunoblastic lymphadenopathy). The patient had a marked response to large doses of corticosteroids with prompt resolution of symptoms. Corticosteroid therapy was inadvertently discontinued, however, with rapid recurrence of the entire syndrome. A right hemiparesis developed complicated by anemia and heart failure, and the patient died, with active disease, five months after the onset of illness.

The third patient (Case 3) presented with marked adenopathy, and a morphologic diagnosis of Hodgkin's disease was made elsewhere. The patient was treated with cyclophosphamide, vincristine and prednisone which resulted in partial remission for one month, followed by recurrent adenopathy, pulmonary infiltrates and hemolytic anemia. A diagnosis of immunoblastic lymphadenopathy was made on review of the lymph node slides. The patient was then treated with large doses of corticosteroids with marked response of symptoms. However, the treatment was subsequently changed to vincristine, doxorubicin and prednisone. The patient received two courses of chemotherapy prior to his final admission with a perforated pyloric ulcer, and subsequently died of Escherichia coli sepsis and terminal disseminated intravascular coagulation five months after the onset of his illness.

The fourth patient (Case 4) presented with lymphadenopathy, rash and angioneurotic edema. The hyperviscosity syndrome developed, and bone marrow infiltrates were noted. A malignant immunoproliferative disorder was diagnosed on a lymph node biopsy specimen (later reclassified as immunoblastic lymphadenopathy). The patient became uremic, thought secondary to ureteral obstruction from paravertebral adenopathy. The hyperviscosity syndrome, uremia and lymphadenopathy responded transiently to the administration of cyclophosphamide, vincristine and prednisone, but the patient died one month after the onset of disease with massive adenopathy, lethargy and marked uremia.



Figure 1. Posteroanterior chest film showing bilateral, basilar, interstitial infiltrates and pleural effusions.

PATHOLOGIC OBSERVATIONS

Lymph Nodes. The nodal architecture was diffusely altered by a mixed cellular proliferation with a prominent component of immunoblasts, accompanied by plasma cells, plasmacytoid lymphocytes and variable numbers of well differentiated lymphocytes (Figure 2). Marked pyroninophilia was present. Eosinophils were present in those patients with a peripheral eosinophilia. Histiocytes were generally present in small numbers, either singly or in small clusters, and were prominent in one patient. A marked proliferation of finely arborizing, small blood vessels was present diffusely, with hyperplasia of the endothelium (Figure 2). Amorphous, acidophilic material was found in small amounts throughout the lymph nodes. The capsule was infiltrated in all cases, with focal involvement of perinodal adipose tissue. Peripheral sinuses were open, but moderately compressed. A few residual germinal centers were present in three patients. No Reed-Sternberg cells, necrosis, fibrosis, vasculitis or granulomas were present in the nodes.

Bone Marrow. Bone marrow smear and biopsy specimens from all patients were examined. The marrow from three patients was normocellular, without focal infiltration. A mild plasmacytosis and an increase in plasmacytoid lymphocytes were noted in all cases. Patients with peripheral eosinophilia also had mild

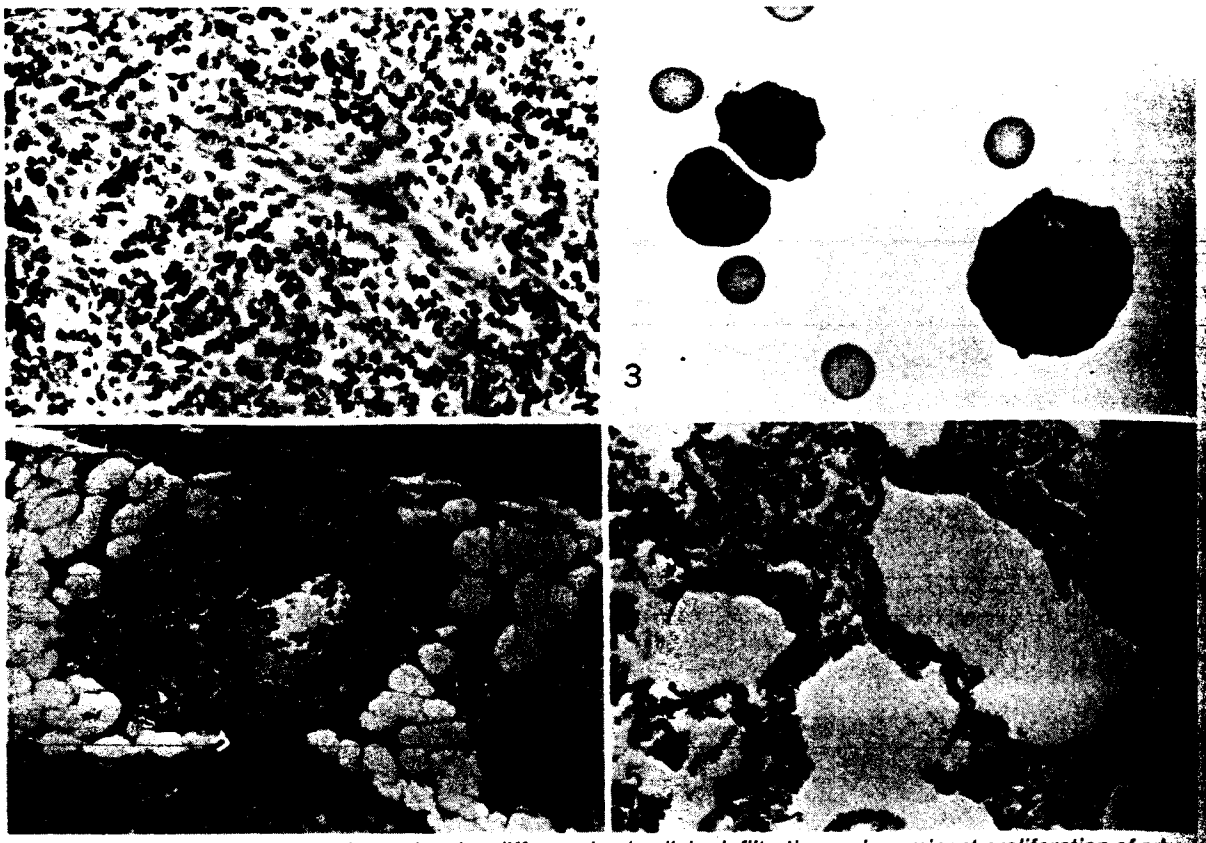


Figure 2. *Lymph node biopsy specimen showing diffuse mixed cellular infiltration and prominent proliferation of arborizing small vessels. Hematoxylin and eosin stain, magnification × 160.*

Figure 3. *Pleural fluid cytology showing a plasmacytoid immunoblast with a large, eccentric nucleus, dispersed chromatin, multiple large nucleoli and abundant basophilic cytoplasm. Also present are 2 plasma cells. Wright's stain, magnification × 400.*

Figure 4. *Muscle biopsy specimen showing a mixed cellular infiltrate surrounding and in the wall of a small arteriole. Hematoxylin and eosin stain, magnification × 40.*

Figure 5. *Lung tissue showing the alveolar septums and interstitium diffusely thickened and infiltrated by lymphocytes, plasma cells, and immunoblasts. Hematoxylin and eosin stain, magnification × 40.*

marrow eosinophilia. Erythroid hyperplasia was present in patients with hemolysis. One patient (Case 4) was atypical in that depleted, focal, paratrabecular infiltrates of lymphocytes, plasma cells, histiocytes and scattered immunoblasts were present, without prominent vascularity.

Pleural Fluid. Pleural fluid was examined in three patients. The cells consisted largely of lymphocytes, plasma cells and eosinophils. Histiocytes were prominent in one patient. Another patient (Case 4) showed a very prominent infiltrate of immunoblasts, plasmacytoid lymphocytes and plasma cells, some with flaming cytoplasm (Figure 3).

Muscle and Skin. Muscle biopsy specimens from two patients showed a marked, mixed cellular infiltrate of lymphocytes, plasma cells, eosinophils and scattered immunoblasts surrounding and in the walls of small arterioles, capillaries and venules (Figure 4). Skin biopsy specimens from these patients had mild perivascular infiltrates of lymphocytes, plasma cells and eosinophils. A skin biopsy specimen from a third patient had moderate perivascular infiltrates of lymphocytes and neutrophils, with neutrophils present in vascular walls. No muscle or skin biopsy was performed on the other patient.

Autopsy Findings. Complete autopsies were performed on two patients (Cases 2 and 3). The lymph nodes in both were similar to those previously described, except that germinal centers were no longer present in one. The bone marrow from one patient was hypercellular with eosinophilia, and multiple, small focal aggregates of plasma cells, lymphocytes and immu-

noblasts were present. The bone marrow from the other patient was hypocellular with increased plasma cells (20 per cent) and with large, hypocellular areas containing scattered plasma cells, lymphocytes and eosinophils. The spleens weighed 250 g and 1,600 g, and were characterized by marked infiltration and replacement of the white pulp by a mixed infiltrate of lymphocytes, plasma cells and immunoblasts. One spleen had prominent vascularity. Mixed cellular portal infiltrates, with preservation of the limiting plate, were present in the liver of both patients. Mild, mixed cellular infiltrates were also present in the adrenal glands and kidneys.

A large, recent cerebral infarct was present in the temporal lobe of the patient with hemiparesis. An oversewn pyloric ulcer, with peritonitis, and diffuse hemorrhages secondary to terminal disseminated intravascular coagulation were present in the other patient.

The lungs of both patients were characterized by marked perivascular and septal mixed cellular infiltrates consisting of lymphocytes, plasma cells and scattered immunoblasts (Figure 5). Alveolar septums were markedly thickened, and alveoli were decreased in size. Scattered hyaline membranes were present in one patient.

OMMENTS

e are not aware of a previous report of patients with mmunoblastic lymphadenopathy who had symptomatic ulmonary infiltrates, hypocomplementemia and vasulitis. Among 56 patients reported on in two large eries [1,2], involvement of the lung was mentioned in ly six instances, a morphologic description was made only one, and no mention of pulmonary symptoms s made. Iseman and associates [3] have recently scribed a patient with immunoblastic lymphadepathy who presented with significant pulmonary mptoms and roentgenographic findings. A lung biopsy ecimen showed a diffuse infiltration of the alveolar eptums and interstitium by immunoglobulin-producing lasma cells, lymphocytes and immunoblasts, very imilar to the cases presented in this paper. Two other eports briefly mention pulmonary symptoms and infiltrates on chest roentgenograms [4,5]. Neither vasulitis nor hypocomplementemia were noted in the two arge series [1,2]. Moore and associates [4] briefly mention the development of vasculitis in one of their 14 patients; this patient required digital amputation, but no morphology is presented. One patient with normal complement levels has been described [6], and complement levels are reported in another [7], but no normal values are given. Only one patient with immunoblastic lymphadenopathy and hypocomplementemia has been described [8], thought to be secondary to circulating immune complexes containing complement.

The clinical similarities of immunoblastic lymphadenopathy to allergic drug reactions and the collagen-vascular diseases are striking. Some morphologic similarity in lymph node biopsy specimens also exists. Diphenylhydantoin-induced lymphadenopathy [9] may closely resemble immunoblastic lymphadenopathy. Lymph node morphology has not been well described in patients with drug reactions other than those taking anticonvulsants. Lymphadenopathy is not uncommon in disseminated lupus erythematosus [10] and can cause diffuse hyperplasia, but focal necrosis and hematoxylin bodies are usually required for more specific histologic diagnosis [10,11]. Arteritis may cause extensive inflammatory changes, granulomas [12] and occasionally vasculitic lesions. No necrosis, hematoxylin bodies, granulomas or vasculitic lesions were present in the lymph nodes from the four patients we describe. No specific collagen disease could be clinically diagnosed, and a history of drug intake prior to the onset of illness was present in only one patient. Allergic angiitis in patients with systemic drug reactions usually involves only small arterioles and venules [13], closely resembling the lesions described in the muscle and skin biopsy specimens from three of our patients.

The etiology of immunoblastic lymphadenopathy is not known. The disease is thought to represent a non-neoplastic proliferation of the B-lymphocyte system [1], perhaps related to an impairment of T-cell regulatory functions [2]. Immunohistologic and ultrastructural studies [6,7] have supported a B-cell orgin for the proliferating cells. Profound depression of circulating T cells [3,6,14] and lymph node T cells [6] also supports this hypothesis, and an antilymphocyte factor has been described in one case [1]. Skin testing with a variety of antigens in our patients suggests that cellular immunity was profoundly altered, as has been reported by others [2,8,14]. Lukes and Tindle [1] have suggested that the reaction may be triggered by certain drugs, and others have reported similar associations [2,4,8]. The finding of tubular cytoplasmic inclusion bodies [6] suggest a possible viral etiology. The close association of frequent exposure to a hog confinement facility with pulmonary symptoms in one of our patients, and the subsequent development of immunoblastic lymphadenopathy shortly thereafter, suggests the inhalation of a toxic agent. Levels of toxic gases and aerosolized particulate matter counts are high in such facilities [15]. The morphologic similarity of lymph nodes from patients with immunoblastic lymphadenopathy to antigenically stimulated lymph nodes, such as postvaccinial lymphadenitis [16] and infectious mononucleosis [17], suggests that patients with immunoblastic lymphadenopathy may be abnormal re-

actors to unknown antigenic agents. Low complement levels and morphologic evidence of vasculitis suggest that circulating immune complexes may be present and responsible for some of the clinical manifestations in immunoblastic lymphadenopathy. Immunoblastic lymphadenopathy may well represent a syndrome, rather than a specific disease, in which the adenopathy is but a nonspecific part of a systemic hyperimmune response to unknown antigens.

Lukes and Tindle [1] have described the morphologic evolution of three of their patients with immunoblastic lymphadenopathy into immunoblastic sarcoma, a neoplasm which has been observed to develop in patients with other chronic abnormal immune disorders [18]. Fischer and associates [5] recently described a similar patient, with a leukemic phase, and presented ultrastructural studies compatible with a B-cell origin. We have also seen a similar patient with malignant transformation [19].

The course of immunoblastic lymphadenopathy is usually progressive, with a reported median survival of 15 months in 18 fatal cases [1]. Another large series [2] reported a rapid course terminating in death in one to 19 months in over half their patients. Good responses to the administration of corticosteroids and combination chemotherapy have been reported [2], but spontaneous remissions have also occurred [1,2]. Levamisole, a stimulant of the T-cell system, has induced a partial remission in one case, with return of T and B cell levels to normal [14]. Many deaths have been related to chemotherapy-induced pancytopenia and infection, and a more conservative approach utilizing supportive treatment and corticosteroids has been suggested [2]. Three of our patients treated with corticosteroids had a marked clinical response. One patient has been in clinical remission for 18 months, whereas another had a relapse and died only after corticosteroid therapy was inadvertently discontinued. A third patient initially responded to corticosteroid therapy, but had a relapse shortly after combination chemotherapy was started and died of gastric perforation, sepsis and pancytopenia. The fourth patient had only a transient response to combination chemotherapy and died shortly thereafter. Our experience also suggests that supportive care and corticosteroids constitute the safest therapeutic approach.

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