

# T lymphocyte proliferation in lymphomatoid granulomatosis<sup>1</sup>

Robert E. Petras, M.D.  
Raymond R. Tubbs, D.O.  
Gordon N. Gephardt, M.D.  
Bruce A. Sebek, M.D.  
Joseph A. Golish, M.D.  
James K. Weick, M.D.

<sup>1</sup> Departments of Pathology (R.E.P., R.R.T., G.N.G., B.A.S.), Pulmonary Medicine (J.A.G.), and Hematology and Oncology (J.K.W.), The Cleveland Clinic Foundation. Submitted for publication Nov 1984; accepted May 1985.

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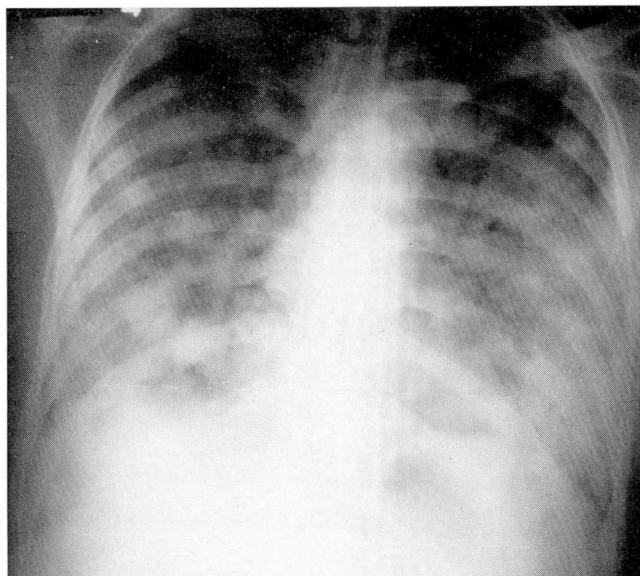
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Four cases of lymphomatoid granulomatosis (LYG) were studied by light microscopy, electron microscopy, and paraffin-section immunohistochemistry for immunoglobulin light chains and muramidase. In two of the four cases, frozen-section immunohistochemistry was performed to demonstrate immunoglobulin light chains, heavy chains, and complement. These two cases were also studied by frozen-section immunohistochemistry using monoclonal antibodies to evaluate the expression of lymphocyte differentiation antigens by the proliferating cells. The pulmonary lesions demonstrated polyclonal light chain immunostaining. However, only a few cells were positive for surface or cytoplasmic immunoglobulin. Cytologically atypical large lymphoid cells invariably contained cytoplasmic immunoglobulin of one light chain type and did not express T lymphocyte differentiation antigens. Most of the infiltrate was composed of T lymphocytes (as demonstrated using monoclonal hybridoma antibodies) and muramidase positive tissue macrophages. No extracellular immune complexes were demonstrated. Based upon these observations, the authors postulate that the early lesions of LYG represent a form of cell-mediated vasculitis which can and usually does progress to a malignant lymphoproliferative disorder which in some cases demonstrate T cell differentiation.

**Index terms:** Lymphomatoid granulomatosis • T lymphocytes

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Lymphomatoid granulomatosis (LYG), a necrotizing pulmonary angiitis, was first described by Liebow et al in 1972.<sup>1</sup> The disease typically affects middle-aged adults, presenting as symptomatic nodular pulmonary radiographic densities. It often involves the skin, central ner-



**Fig. 1.** Chest radiograph exhibiting confluence of bilateral nodular opacities with accentuation toward bases and absence of hilar adenopathy.

vous system, and kidneys. The high mortality from LYG is usually attributable to pulmonary insufficiency. An overt malignant lymphoma develops in approximately 15% to 18% of patients, most of which have been classified as immunoblastic sarcoma.<sup>1-4</sup> Angiocentric lesions dominate the histopathologic appearance and are characterized by an angiodestructive cellular infiltrate reported as unique to this disease.<sup>1</sup> The cellular infiltrate is polymorphous, comprised of an admixture of small lymphocytes, plasma cells, plasmacytoid cells, tissue macrophages, and immunoblasts which are often cytologically atypical and are the hallmark of the disease. LYG has certain characteristics in common with Wegener's granulomatosis, other systemic vasculitides, malignant lymphoma, and midline malignant reticulosis (MMR).<sup>1-12</sup> DeRemee et al<sup>6</sup> suggest that LYG and MMR may actually represent the same disease process.

In order to further evaluate the vasculitis of LYG, we performed frozen-section immunohistochemistry and immunofluorescence for immunoglobulin heavy chains and complement in two cases. Because of the relationship of LYG to malignant lymphoma, frozen-section immunohistochemistry for surface immunoglobulin light chains and T lymphocyte differentiation antigens was performed in two cases. In addition, paraffin-embedded fixed tissue was studied for cyto-

plasmic immunoglobulin light chains and mu-ramidase in all four cases.

## Case reports

**Case 1.** A 38-year-old woman presented with a two-week history of cough, malaise, nausea, vomiting, and diarrhea, as well as 30-lb weight loss over six months. Four days prior to admission, she became dyspneic, febrile, and hemoptysis developed. She presented with severe respiratory distress, fever (102.2 °F), and microscopic hematuria. The chest radiograph revealed subtotal opacification of both lung fields by irregular nodular densities without hilar lymphadenopathy (*Fig. 1*). Open lung biopsy demonstrated lesions typical of LYG. She became progressively worse and died of respiratory insufficiency five days after admission. An autopsy was performed.

**Case 2.** A 64-year-old woman presented with an eight-month history of nausea, vomiting, and 60-lb weight loss. A brother had pulmonary tuberculosis, and the patient was PPD positive. The chest radiograph revealed a left pleural effusion and multiple nodular mass densities in the left base without hilar lymphadenopathy. Aspiration cytology revealed a few atypical lymphoreticular cells, but was not diagnostic. An open lung biopsy was performed and a diagnosis of LYG established. The patient was treated with prednisone and antituberculous therapy. The subsequent chest radiograph was normal. Steroids were tapered, and she was free of disease 37 months after diagnosis.

**Case 3.** A 39-year-old man presented with cough, weakness, malaise, hepatosplenomegaly, and 60-lb weight loss. An erythematous skin rash had been present three months prior to the onset of the pulmonary symptoms. The chest radiograph revealed multiple nodular mass densities bilaterally, more prominent in the bases, without hilar lymphadenopathy. Skin biopsy findings revealed necrotizing dermal vasculitis. Open lung biopsy was performed and initially was interpreted as Hodgkin's disease. The patient received six courses of MOPP therapy. The lung densities persisted, and the skin rash returned. An abdominal mass developed, and biopsy findings were again interpreted as Hodgkin's disease. However, review of histologic sections from the lung and abdominal mass demonstrated lesions typical of LYG. The treatment regimen was changed to methyl CCNU. Two and one half years after the onset of therapy, the chest radiograph was normal, as were liver and bone marrow biopsies. Acute myelogenous leukemia developed and the patient died eight years following his original presentation. An autopsy was not performed.

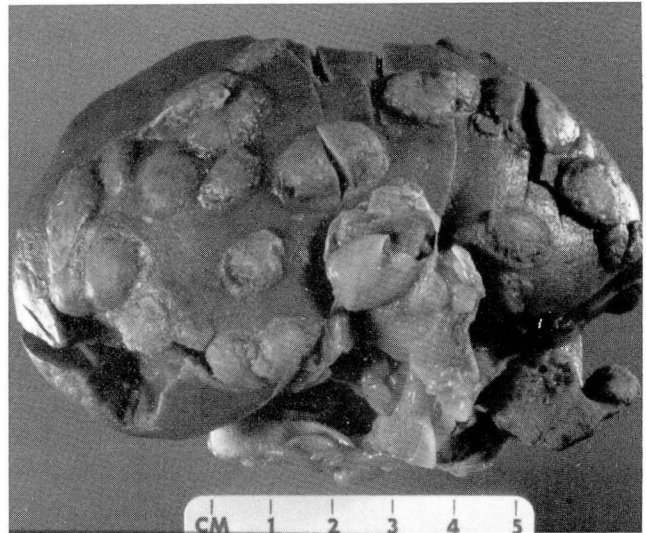
**Case 4.** A 46-year-old man presented with a two-month history of fever, productive cough, fatigue, diaphoresis, and rectal bleeding. The physical examination revealed a cutaneous ulcer on the medial aspect of the right thigh. There were no palpable lymph nodes. The chest radiograph showed multiple bilateral nodular pulmonary mass densities, some of which were cavitating, more prominent in the bases, without hilar lymphadenopathy. The tuberculin skin test and fungal serology were negative. Antinuclear antibody titre was positive in a dilution of 1:80. Open lung biopsy

was performed and material obtained was diagnostic of LYG. Subsequent studies showed the patient to have microscopic hematuria and bilateral renal mass lesions, as demonstrated by computed tomography. Clusters of atypical cells identical in appearance to the atypical cells seen in the pulmonary vessels and parenchyma were also identified in the bone marrow. After an initial response to chemotherapy with cytoxan, adriamycin, vincristine, and prednisone, a generalized skin rash developed, as well as peripheral neuropathy, and finally generalized seizures. He died six months after diagnosis. Permission for autopsy was denied.

### Methods and materials

Involved tissue by gross inspection was submitted for multiparameter evaluation. Tissue segments 1.0 x 1.0 cm from the first and fourth patients described here were snap-frozen in isopentane at  $-150^{\circ}\text{C}$  in liquid nitrogen and mounted on a chuck. Thick segments of representative tissue (1–2 mm) from all 4 patients were fixed in abundant volumes of neutral buffered formalin, Bouin's solution, and zinc-substituted Zenker's solution for routine histochemistry and paraffin-embedded immunohistochemistry. Tissue from the first and fourth patients, consisting of 1.0-mm<sup>3</sup> cubes was fixed in buffered glutaraldehyde and submitted for electron microscopy, post-fixed in osmium tetroxide, dehydrated in graded alcohols, and embedded in Spurr. Appropriate blocks were then thin sectioned and stained with lead citrate and uranyl acetate and examined in an RCA EMU4 transmission electron microscope.

Fresh-frozen and paraffin-embedded immunohistochemistry for surface and cytoplasmic immunoglobulins and muramidase were done as previously described.<sup>13–15</sup> Fresh-frozen direct immunofluorescence and immunohistochemistry were also done. Briefly, fresh-frozen 4–6- $\mu$  sections were air-dried and were incubated with fluorescein- or peroxidase-labeled rabbit antibody with specificity against human light and heavy chains and C3 for 20 minutes. Immunofluorescence slides were washed and mounted with 90% glycerol in phosphate-buffered saline (PBS) and examined under the Leitz fluorescent microscope. Immunoperoxidase reaction product was developed in Hanker-Yates reagent (p-phenylenediamine and pyrocatechol, HYR). For identification of immunoglobulin light chains, fresh frozen 4–6- $\mu$  sections were air-dried and monospecific peroxidase conjugated rabbit anti-human  $\kappa$  light chains and antihuman  $\lambda$  light chains (Dako) were overlaid on the tissue and

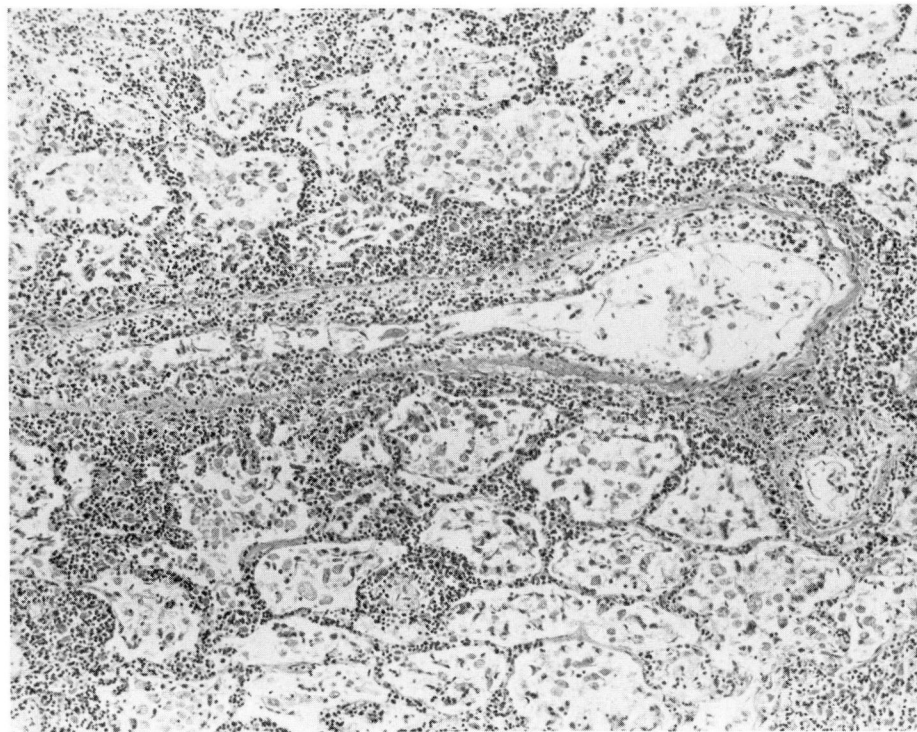


**Fig. 2.** Bulging mass lesions of lymphomatoid granulomatosis involving kidney.

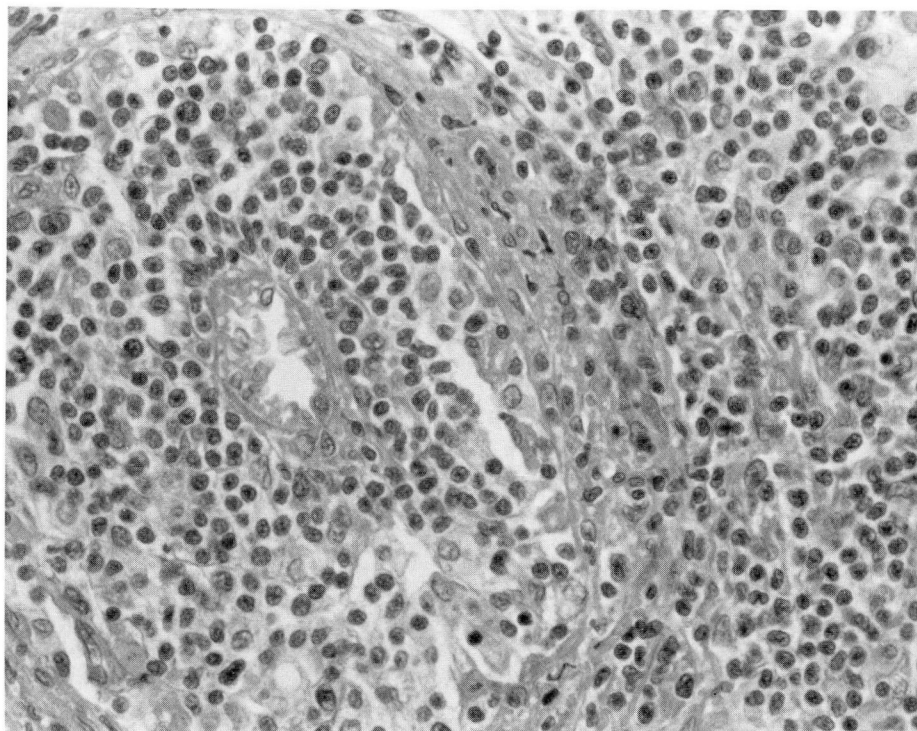
allowed to incubate for 10 minutes. Slides were washed in three changes of PBS and one change of 0.1 M Tris HCl (pH, 7.6) for 30 seconds and the color reaction product developed using HYR. Sections were subsequently dehydrated and mounted with Permount.

Paraffin-embedded tissues were evaluated in a similar manner. Sections were deparaffinized, rehydrated, and endogenous peroxidases blocked with 6% hydrogen peroxide in absolute methanol for one hour. Normal goat serum and subsequently peroxidase-conjugated anti- $\kappa$  and anti- $\lambda$  antibodies were overlaid on the sections for one hour. In addition, sections were also stained with the unlabeled peroxidase-antiperoxidase immunoperoxidase technique for cytoplasmic immunoglobulins and cytoplasmic muramidase. All sections were subsequently dehydrated and mounted with Permount following hematoxylin counterstain.

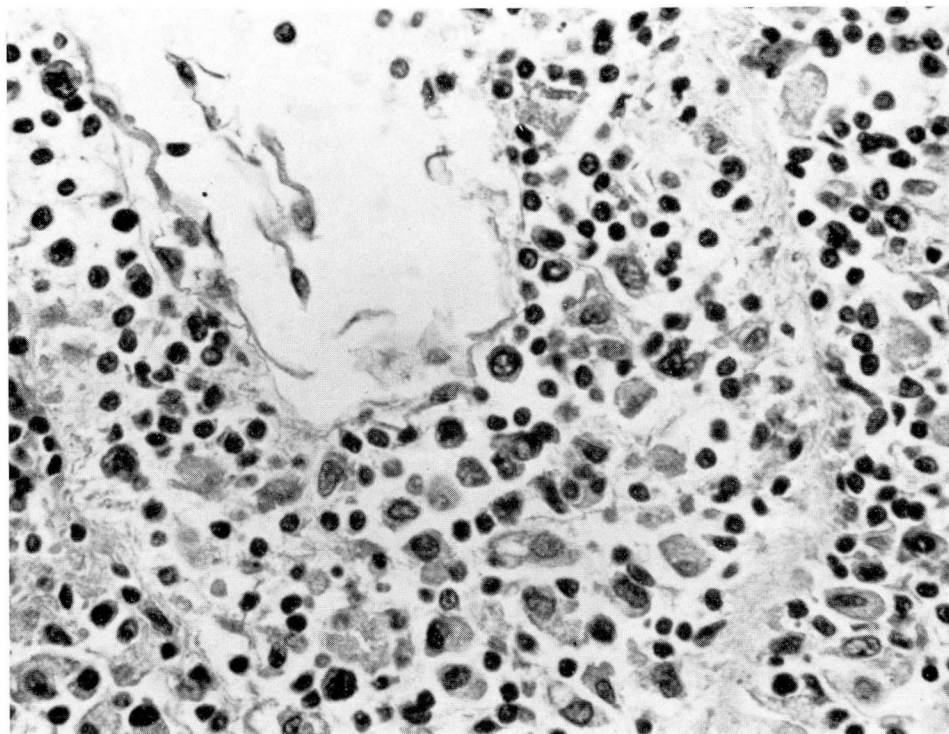
For identification of lymphocyte differentiation antigens,<sup>16</sup> fresh-frozen 8- $\mu$  sections were allowed to air dry and fixed for 10 minutes in acetone. After washing in PBS, the sections were incubated with monoclonal hybridoma antibodies having specificity for peripheral blood T cells (OKT3. Pan), T suppressor/cytotoxic cells (OKT8. Sup), and T inducer/helper cells (OKT4. Ind) for two hours (Ortho). Slides were then washed in PBS and affinity-purified peroxidase conjugated goat anti-mouse IgG applied



**Fig. 3.** Photomicrograph of pulmonary lesion from Case 1, demonstrating angiocentricity of the cellular infiltrate (hematoxylin and eosin,  $\times 64$ ).



**Fig. 4.** Photomicrograph of pulmonary vessel from Case 4. The angiodestructive infiltrate is not associated with fibrinoid necrosis. Small, atypical "squiggly" lymphocytes predominate in the polymorphous infiltrate, but tissue macrophages, plasma cells, and rare, atypical immunoblasts are also present (hematoxylin and eosin,  $\times 400$ ).



**Fig. 5.** High magnification of angiodestructive pulmonary lesion from Case 1. The infiltrate is polymorphous. There is no fibrinoid necrosis. In addition to small atypical lymphocytes, tissue macrophages and atypical immunoblasts are prominent (hematoxylin and eosin,  $\times 400$ ).

and incubated at room temperature for 30 minutes. Slides were again washed in PBS and the color reaction product developed using HYR. After hematoxylin counterstain, the sections were dehydrated and mounted with Permount.

## Results

### *Gross findings*

In Case 1, autopsy demonstrated changes in the lungs and kidneys similar to those described by Liebow et al.<sup>1</sup> All pulmonary lobes were involved by nodular masses which became confluent, were gray-pink in color, and nonencapsulated. Cavitation was present in the left lower lobe. The kidneys showed multiple rounded and wedge-shaped pale pink masses which bulged from the capsular surfaces (*Fig. 2*).

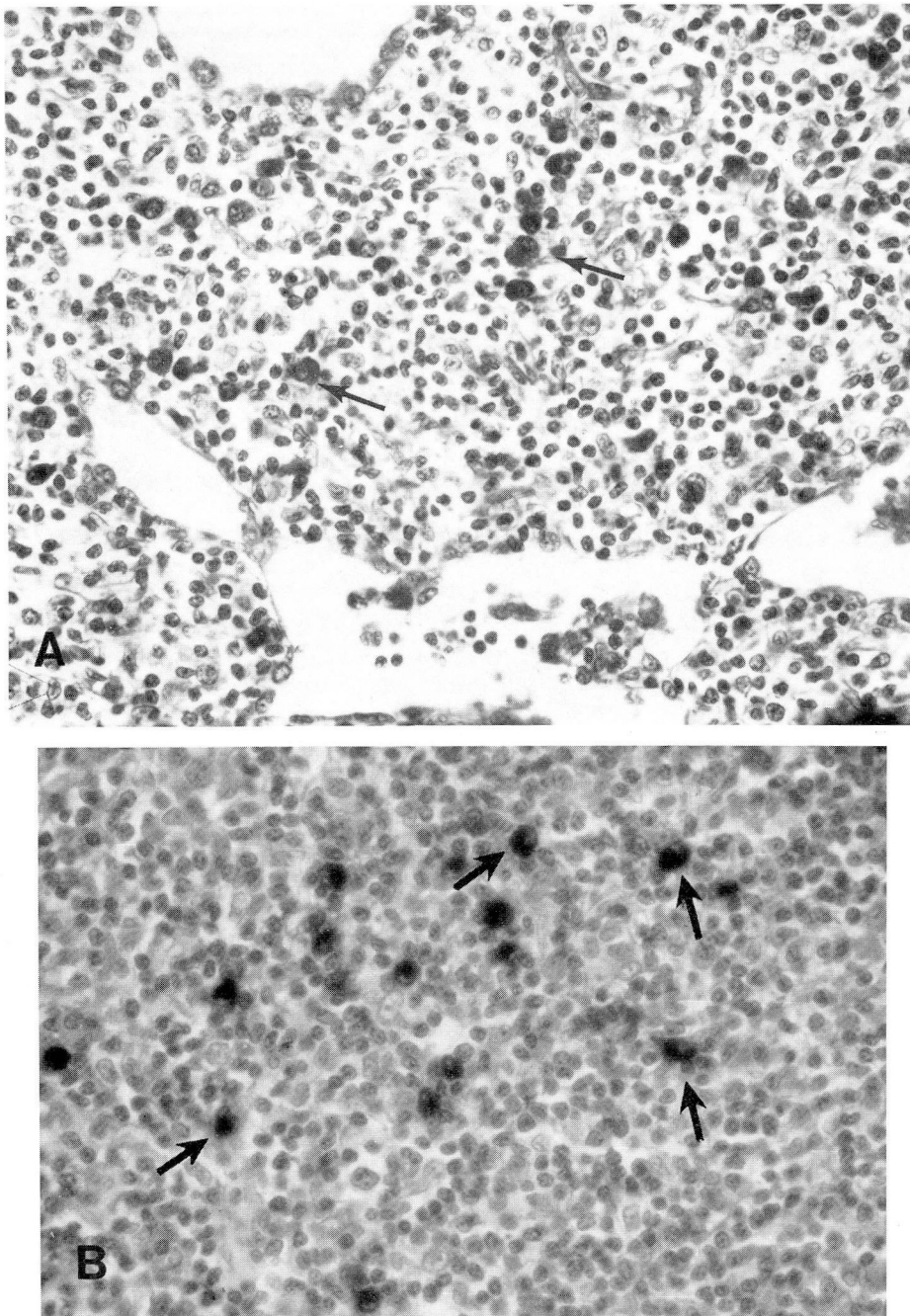
### *Light microscopy*

Light microscopy of the lungs in all four cases revealed typical angiocentric and angiodestructive lesions of LYG (*Figs. 3–5*). Transmural inflammation of pulmonary arteries and veins was present as well as infiltration of alveolar septae.

The infiltrate was polymorphous, consisting predominately of small twisted “squiggly” lymphocytes. Plasma cells, plasmacytoid lymphocytes, tissue macrophages, and cytologically atypical immunoblasts were also present. Areas of necrosis were present in all four cases. The mitotic rate in Cases 1 and 3 was high. Case 2 was unique in that there was a paucity of atypical immunoblasts. Cases 3 and 4 showed extensive areas of necrosis with large numbers of atypical immunoblastic cells. The histopathology of Case 3 yielded no Reed-Sternberg cells. Review of the skin biopsy in Case 3 showed necrotizing dermal vasculitis with occasional atypical mononuclear cells. The anterior abdominal wall mass as well showed areas of necrosis with vasculitis and a polymorphous infiltrate similar to the pulmonary lesion. Case 1 showed characteristic microscopic lesions of LYG in the brain, mesentery, and kidney, as well as the typical lung lesions.

### *Immunofluorescence/immunohistochemistry*

Direct immunofluorescence and immunoperoxidase on fresh-frozen tissue in Cases 1 and



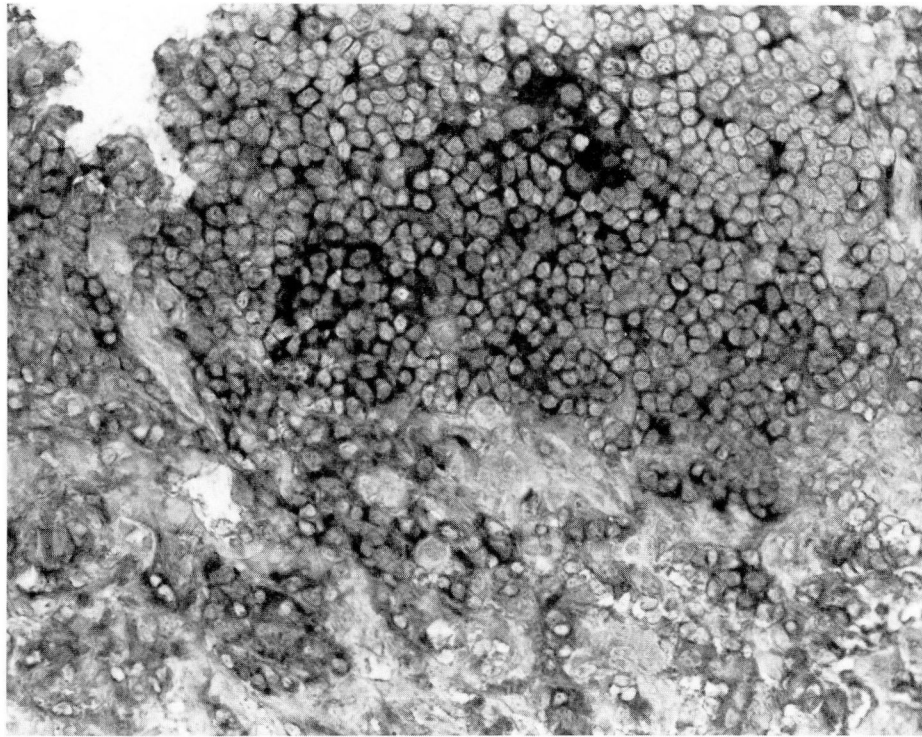
**Fig. 6. A.** Photomicrograph showing positive immunostaining for  $\kappa$  light chains within plasma cells and immunoblast.

**B.** This photomicrograph demonstrates positive immunostaining for cytoplasmic  $\lambda$  light chains.

(Immunoperoxidase with hematoxylin counterstain,  $\times 400$ ).

4 were negative for extracellular deposits of IgM, IgG, IgA, and C3. In all cases, occasional plasma cells and lymphocytes demonstrated polyclonal cytoplasmic immunoglobulins, using both fresh-

frozen section and paraffin-embedded material; however, only about 5% of the cellular infiltrates exhibited positive cytoplasmic and/or surface immunostaining for light chains. The cytologically



**Fig. 7.** Photomicrograph, cryostat frozen section immunohistochemistry, pulmonary vascular infiltrate. Numerous T lymphocytes are present, identified with mouse monoclonal antibody specific for peripheral T lymphocytes (immunoperoxidase with hematoxylin counterstain,  $\times 400$ ).

atypical immunoblasts also stained in a polyclonal fashion (*Fig. 6*) invariably contained cytoplasmic immunoglobulin of one light chain type, were muramidase negative, and did not express T lymphocyte differentiation. In Cases 1 and 4, isolated clusters of  $\kappa$  positive (Case 1) and  $\lambda$  positive (Case 4) B immunoblasts were identified. In each case, these clusters were formed by approximately 20 "atypical" cells. Approximately half of the remaining cells in the infiltrates were lymphocytes which stained with monoclonal antibody identifying peripheral blood T cells (OKT3) (*Fig. 7*). Most of these T cells were of the cytotoxic/suppressor subset, identified by predominant staining with OKT8, with very few of the T lymphocytes positive with OKT4 which identifies the helper/inducer subset. Tissue macrophage made up the remaining half of the polymorphous cellular infiltrates and clearly demonstrated intracytoplasmic muramidase.

#### *Electron microscopy*

Electron microscopy was performed in Cases 1 and 4. The infiltrate consisted of an admixture

of lymphocytes with irregular nuclear contour, tissue macrophages, immunoblasts, and rare plasma cells. No extracellular electron dense deposits or viral particles were identified.

#### **Discussion**

The similarities and differences between LYG and other forms of systemic vasculitis have been extensively reviewed.<sup>1,3,9,17-19</sup> Fibrinoid necrosis and exudation often characterize the vascular lesions in Wegener's granulomatosis.<sup>17,20</sup> Polyarteritis nodosa and other systemic vasculitides thought to be of immune complex etiology also show similar histology.<sup>20,22</sup> In contrast, the histology of the LYG vascular lesion is peculiar.<sup>5-8,17,19,23</sup> It shows an infiltrative pattern of angiodestruction. Thrombosis, fibrinoid necrosis, and giant cell reaction are notably absent. We were unable to show extracellular immune complex deposits in the lesions. The lack of demonstrable immune complexes in the lesions along with the unusual histologic appearance strongly suggest that the vasculitis is not of humoral, autoimmune pathogenesis. Cell-mediated immunity may bet-

ter explain the histopathologic and immunohistologic observations. We noted a striking predominance of T8 positive cells in the inflammatory infiltrate. This predominance of T8 positive cells has also been identified in the peripheral blood in patients with LYG.<sup>24</sup> It has recently been shown that in human renal allograft rejection, mononuclear cells invading blood vessels contain numerous T8 positive cells, supporting a role for cytotoxic T cells in this type of vascular injury.<sup>25</sup> It is theoretically possible for cytotoxic T cells to attack the host's own vascular cells if their surfaces were altered by viral infection or drugs.<sup>22</sup>

Some authors have proposed that LYG represents a form of malignant lymphoma.<sup>10,26-28</sup> In this study, we have shown that the infiltrate stains in a polyclonal reactive pattern rather than a monoclonal neoplastic pattern for surface and cytoplasmic immunoglobulin light chains both by paraffin-embedded immunohistochemistry and frozen-section immunohistochemistry. Our work verifies and validates work reported by Bender et al,<sup>11,12</sup> done only on paraffin-embedded fixed tissue and by Kapanci and Toccanier<sup>29</sup> done with both frozen and paraffin-embedded tissue sections. We also showed that the large atypical lymphoreticular cells, considered the hallmark of the disease, invariably contain cytoplasmic light chains and also stained in a polyclonal fashion. It is our impression that these cells represent B-cell immunoblasts. Very few cells in the inflammatory infiltrate in our cases showed B-cell markers. Our findings of polyclonality tend to rule out B-cell lymphoma in our four cases. Review of the literature documents cases of monoclonal B-cell lymphomas arising in LYG,<sup>11,30</sup> and in one study, multiple biopsies performed in 3 patients showed progression of disease from a polyclonal to a monoclonal staining pattern for surface immunoglobulin.<sup>29</sup>

Nichols et al<sup>31</sup> have stated that LYG may represent a form of T-cell malignant lymphoma. The presence of a polymorphous infiltrate with an abundance of tissue macrophages, along with widespread visceral involvement, are all characteristics of T cell lymphomas.<sup>31-35</sup> Our marker studies correlate well with the solitary case reported by Nichols et al<sup>31</sup> and document that a large proportion of the proliferating cells are of T cell origin. Costa et al<sup>33</sup> recently reported peripheral T lymphocyte markers in the neoplastic cells in 1 patient from a series of 4 who had striking histiocytic erythrophagocytosis associ-

ated with a pulmonary vasculitis containing atypical lymphoid cells. The authors believed that these lesions represented peripheral T cell lymphoma involving the lung. These same authors included these cases in a review of their prospective clinical and therapeutic experience with LYG.<sup>36</sup>

We have downplayed somewhat the apparent predominance of OKT8 positive cells in our cases. Our experience has shown that the amount of T4 antigen expressed on the T helper/inducer cells tends to be much less than T8 expression in the T suppressor/cytotoxic lymphocytes. This fact could lead to the underestimation of the number of T4 positive cells in the infiltrates. Also, the predominance of a T cell subset cannot be used as a marker of neoplastic proliferation as selective proliferation of helper or suppressor T cell subsets can be seen in certain reactive autoimmune diseases.<sup>37-41</sup> Recently, predominance of T4 positive cells has been reported in the skin lesions of LYG by immunofluorescence.<sup>42</sup> This study must be looked at with some reservation. It is known that macrophages in dermal infiltrates may also mark using antibody directed against T4.<sup>43</sup> Also, with immunofluorescence, individual cell morphology is difficult or impossible to ascertain. These two points could have led to an overestimation of the number of T4 positive cells in their case.

Malignant lymphoma cannot, however, explain the clinical findings in all reported cases of LYG. There are cases in the literature where patients with LYG histology have recovered with inadequate therapy or with antibiotics alone.<sup>9,27</sup> Also, there are rare cases of apparent spontaneous recoveries.<sup>9</sup> This clinical behavior would be unusual for a malignant lymphoproliferative disorder.

Although LYG is intimately associated with malignant lymphoma, we believe all cases cannot and should not be classified as malignant lymphoma. We agree with the views of Kapanci and Toccanier<sup>29</sup> and Fauci et al<sup>36,44</sup> who believe that the different clinical courses represent different points on a continuum of disease histologically identified as LYG. The evidence in the literature,<sup>9,11,12,29,31</sup> as well as our own results, tends to strengthen views promulgated by Leibow et al<sup>1</sup> and Crissman.<sup>5</sup> The disease could represent an abnormal immune response to a yet unknown antigen or to a host antigen altered by drugs or virus. It primarily manifests as a cell-mediated



vasculitis with a propensity for the upper and lower respiratory tract vasculature. Differences in genetic immunoregulation could account for the differences in clinical course. A very small group, able to handle the antigenic stimulation, could explain the apparent spontaneous cures. Progressive pulmonary insufficiency secondary to cell-mediated vasculitis develops in those unable to handle this challenge. This accounts for the majority of deaths. Finally, an overt malignant lymphoproliferative disorder, which can be either B or T cell in derivation, may subsequently develop in some patients.

It is clear that additional work must be done. Pretreatment immunologic status, including HLA-Dr typing, should be investigated. Also, pathologists must make greater efforts to preserve tissue for study. We advocate the development of a standardized protocol for processing open lung biopsies. This should include complete microbiologic workup, frozen-section consultation to ensure adequacy of the specimen, and the routine processing of tissue for light and electron microscopy. We also recommend securing tissue for frozen-section immunohistochemistry and/or cell suspension studies so that complete immunologic phenotyping can be performed in those cases where LYG or malignant lymphoma enter into the differential diagnosis.

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Robert E. Petras, M.D.  
Department of Pathology  
The Cleveland Clinic Foundation  
9500 Euclid Ave.  
Cleveland OH 44106

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