

Pulmonary Lymphomatoid Granulomatosis Presenting with Neuropathy and Renal Nodules

Vikas Pathak, MD; Govinda Aryal, MD; Lawrence H. Clouse, MD

ABSTRACT

Pulmonary lymphomatoid granulomatosis is a rare diagnosis that frequently presents with a constellation of seemingly unrelated signs and symptoms. It can present with bilateral pulmonary nodules, subcutaneous skin nodules, renal nodules, and peripheral neuropathy. Its protean manifestation, both clinically and radiologically, may delay a definitive diagnosis. We present the case of a patient who had thoracotomy twice and waited for nearly a year to get the final diagnosis because of the presence of a variety of seemingly unrelated symptoms.

CASE PRESENTATION

A 55-year-old man presented with a 4-week history of bilateral chest wall pain. He denied any history of cough, fever, dyspnea, hoarseness, diaphoresis, rash, recent chest trauma, or exposure to respiratory illnesses. He had no pre-existing lung disease and was taking no medications. He smoked a half-pack of cigarettes per day for 30 years, had no history of alcohol or drug abuse, and no contributory family history.

Physical examination and laboratory studies (including complete blood count and complete metabolic panel) were normal. Rib views were normal, but a chest radiograph suggested an abnormality in the left lower lobe. Computed tomography scan (CT) of the chest demonstrated a 2.5 cm mass adjacent to the left diaphragm with small satellite nodules (Figure 1A). Pulmonary function testing showed borderline restriction

• • •

Author Affiliations: Department of Internal Medicine, Marshfield Clinic, Marshfield, Wis (Pathak); Department of Oncology/Hematology, Marshfield Clinic, Marshfield, Wis (Aryal, Clouse); Pulmonary Disease and Critical Care Medicine, University of North Carolina School of Medicine, Chapel Hill, NC (Pathak).

Corresponding Author: Vikas Pathak, MD, Pulmonary Disease and Critical Care Medicine, University of North Carolina School of Medicine, 130 Mason Farm Rd, Chapel Hill, NC 27599; phone: 919.966.7013; e-mail drvikaspathak@gmail.com.

with total lung capacity and vital capacity both around 80% predicted. The mass was resected via thoracotomy, with pathologic material described as “lymphoplasmacytic and noncaseating granulomatous pneumonitis with atypical lymphoid infiltrate.” It did not meet criteria for B-cell lymphoma, as there were few B-cells in the infiltrate and plasma cells

were not light chain restricted. There was no definite diagnosis.

The patient continued to have painful chest wall neuropathy requiring gabapentin and opioids. Magnetic resonance imaging (MRI) of the thoracic spine and brain were normal. A repeat chest CT 4 months later showed postoperative changes and a possible new small (<1 cm) contralateral lower lobe pulmonary nodule adjacent to the pleura.

The patient was referred to neuro-oncology. A lumbar puncture and paraneoplastic antibody panel were normal. Electromyogram and nerve conduction studies demonstrated axonal polyradiculoneuropathy. Although there was no significant demyelination, the pattern was suggestive of chronic inflammatory demyelinating polyneuropathy. He was started on prednisone and intravenous immune globulin. The painful chest wall neuropathy improved but did not resolve completely.

One year later, the patient presented with right flank pain. A chest CT showed innumerable bilateral lung nodules and masses in a lower lobe predominant pattern. Some were round, but many were irregular. (Figure 1B). The CT also showed peculiar kidney mottling. Pulmonary function testing showed a mild restrictive pattern with FEV1/FVC, total lung capacity, and diffusing capacity of the lung for carbon monoxide all 70% to 73% predicted. Open lung biopsy was repeated on the right lung.

Histopathological slides revealed blood vessel injury accompanied by nodules of lymphocytes and plasma cells with relatively large areas of necrosis. Capillaritis was not detected. Necrosis was ischemic in appearance rather than coagulative. Histiocytes and giant cells were present, but were relatively

CME

CME available. See page 65 for more information.

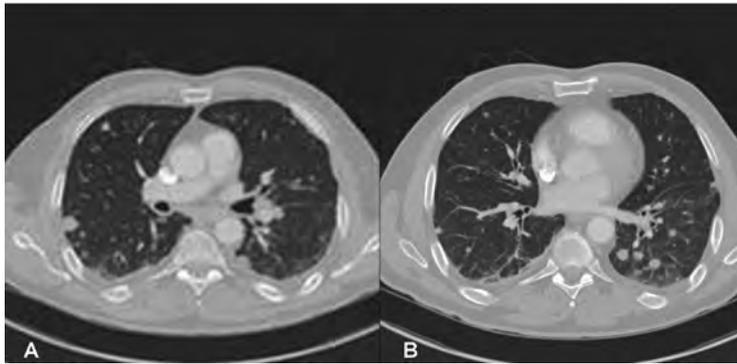


Figure 1: Chest CT demonstrating (A) a 2.5 cm mass adjacent to the left diaphragm with small satellite nodules; (B) innumerable bilateral lung nodules and masses in a lower lobe predominant pattern.

rare. There was sclerosis and obliteration of veins and arteries. Rather than vasculitis, the lesion was an angiocentric B-cell lymphoma.

DNA was extracted from the tissue for B-cell gene rearrangement studies by polymerase chain reaction (PCR). Reactions for Framework 3, Kappa 1, and Kappa 2 all showed a clonal pattern, consistent with the morphologic diagnosis of lymphoma. Immunohistochemical staining showed Epstein-Barr virus (EBV) involvement of scattered B-cells (Figure 2). Based on histopathological examination of the biopsy, the patient was diagnosed with having pulmonary lymphomatoid granulomatosis (EBV-positive diffuse large B-cell lymphoma).

Subsequent staging included a normal head CT (we were unable to do a brain MRI due to recent metallic clips in his chest), a positron emission tomography (PET)/CT scan that showed many of the nodules had only moderate FdG glucose SUV intensity 2.7 to 6.8 (many of the nodules were FdG-negative), and a normal resting cardiac ejection fraction of 74%. The patient declined a bone marrow biopsy. A vascular port was placed, and he was started on chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). Marked improvement was noted on a PET/CT scan after 2 cycles of treatment.

DISCUSSION

First described as a clinicopathologic entity by Averill Liebow and colleagues in 1972,¹ pulmonary lymphomatoid granulomatosis (PLG) is an uncommon multi-organ systemic disease with a predilection for the lungs, characterized by multiple pulmonary nodular lesions with lymphocytic invasion of vascular walls on biopsy. The World Health Organization classification

scheme places lymphomatoid granulomatosis under the generic heading of B-cell proliferations of uncertain malignant potential.² Lymphomatoid granulomatosis is generally considered a B-cell lymphoma with an associated exuberant, benign T-cell reaction. It is described as an extranodal, angiocentric, T-cell rich, B-cell lymphoma. The prominent T-cell component is polyclonal and reactive.

The pathogenesis of lymphomatoid granulomatosis is unknown. These lymphoproliferative disorders are in the family of EBV-associated B-cell lymphomas.² Recent studies using a combination of PCR and in situ hybridization show that most lymphomatoid granulomatosis cases have malignant B-cells containing EBV RNA.

EBV infection causes continuous growth of infected B-cells. When carefully evaluated clinically, most patients with PLG have defects in cytotoxic T-cell function and reduced levels of CD8+ T-cells; this leads to unchecked growth as immune responses cannot stop this growth.³ In addition, PLG can be seen in patients with an underlying immunodeficiency such as AIDS, Wiskott-Aldrich syndrome, and post-transplantation immunodeficiency or other lymphoproliferative disorder.^{4,5} In immunodeficient states, the host's defenses are unable to curb EBV-induced B-cell proliferation. These immune defects may lead to an abnormal host response to EBV infection, resulting in lymphomatoid granulomatosis rather than clearance of the viral infection.³ PLG has been reported in patients being treated with azathioprine and methotrexate,^{6,7} implying defective immune response in clearing EBV-infected cells.

Although PLG can affect patients at any age, the incidence peaks in the 30 to 50 year age range. It is seen predominantly in men, with an estimated male to female ratio of at least 2:1.2 The lung is the most commonly involved organ (>90%),² while the skin (50%), kidney (32%), and neurologic system (30%) may be affected concurrently or independently.^{2,4} The liver, lymph nodes, spleen, and bone marrow usually are spared until late in the course of the illness.² Cough (60%) and dyspnea (30%) are the most common presenting symptoms in patients with lung involvement. Patchy, occasionally painful, erythematous macules, papules, and plaques typically involve the gluteal regions and extremities.⁸ Extensive lymphocytic infiltration of the meninges, cerebral vessels, and peripheral nerves is found in as many as 25% of patients. Peripheral nerve involvement may include distal sensory neuropathy or mononeuritis multiplex.

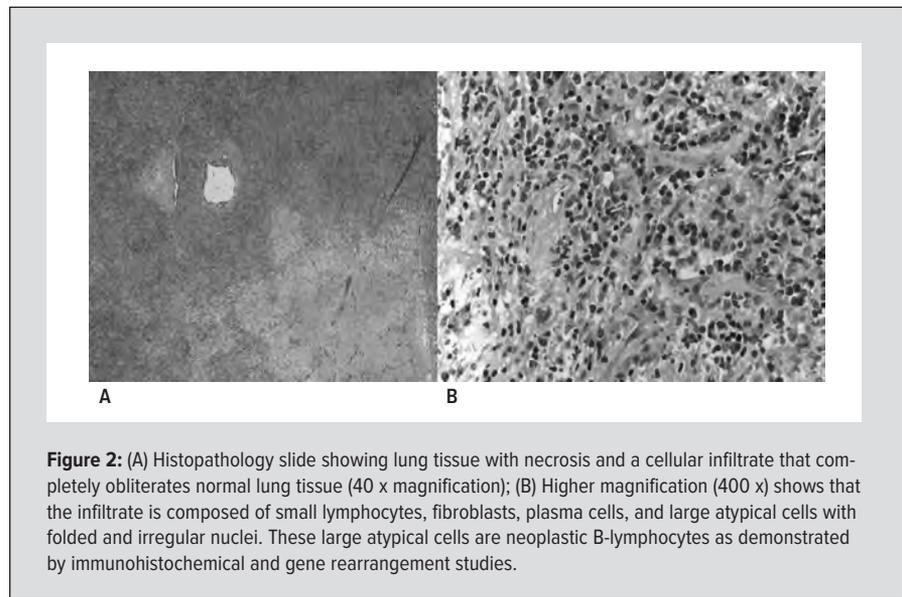
Systemic presentation of lymphoma-related B symptoms in patients include fever (60%), weight loss (35%), and malaise (35%).³ Rarely, patients may be asymptomatic.

Generally, physical examination of the lungs is normal and laboratory studies are nondiagnostic. No characteristic pulmonary function test abnormalities have been reported.⁹ Chest radiography typically reveals multiple poorly defined nodules and/or masses in the mid- and lower-lung zones. Diffuse reticular abnormalities also may be present.^{2,5} Chest CT usually shows both well-defined and poorly-defined nodules throughout both lungs. Most lesions are less than 1 cm in diameter, but larger cavitory masses have been reported.^{10,11} The EBV-positive B-cells typically express CD20 and may express CD30. The background lymphocytes are CD3-positive T-cells which more often express CD4 than CD8.²

A definitive diagnosis of lymphomatoid granulomatosis requires the presence of the following histological triad: polymorphic lymphocytic infiltrate (nodular polymorphic lymphoid infiltrate composed of small lymphocytes, plasma cells, and variable numbers of large atypical mononuclear cells); angiitis due to transmural infiltration of arteries and veins by lymphocytes (a process distinct from vasculitis in which acute and chronic inflammatory cells are found with associated vessel wall necrosis); and granulomatosis (central necrosis within the lymphoid nodules and not granuloma formation).

The therapeutic approach and optimal management have not been well-defined. In several studies, therapy has ranged from observation to treatment with chemotherapy.^{3,5,8,11} Patients with PLG are treated as diffuse large B-cell lymphoma (DLBCL, which includes 4 chemotherapeutic agents including cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Rituximab, a monoclonal antibody directed to the CD20 antigen on B-cell lymphoma cells, also has been used. The addition of rituximab therapy has shown to improve outcomes in these patients.¹² Interferon-alpha2b is the other agent that has been used successfully to induce remission in PLG. There have been some case reports and case series that have demonstrated improved clinical outcomes following treatment with interferon-alpha 2b.¹³⁻¹⁵

The prognosis for PLG is variable. Katzenstein et al⁴ reported on a clinicopathologic study of 152 cases who were



thought to have PLG. Ninety-four of 148 patients with complete follow-up data (63.5%) died. The median survival was 14 months. Patients less than age 25 years, those with neurologic involvement, and those having hepatosplenomegaly, had worse outcomes; while asymptomatic patients and patients with unilateral lesions had more favorable outcomes. Approximately 20% of patients achieved clinical remission without treatment.

CONCLUSION

In patients presenting with pulmonary nodules, peripheral neuropathy and renal nodules, PLG should be considered in the differential diagnosis. PLG is a form of lymphoproliferative disorder, and it can be seen in patients with an underlying immunodeficiency. The histological triad of polymorphic lymphocytic infiltrate, angiitis, and granulomatosis is necessary for diagnosis.

Acknowledgments: The authors thank Bruce Krawisz, MD, Marshfield Clinic, Lab-Pathology for providing the histopathological slides. They also thank Marie Fleisner of the Marshfield Clinic Research Foundation for editorial assistance in the preparation of this manuscript.

Financial Disclosures: None declared.

Funding/Support: None declared

Planners/Reviewers: The planners and reviewers for this journal CME activity have no relevant financial relationships to disclose.

REFERENCES

1. Liebow AA, Carrington CR, Friedman PJ. Lymphomatoid granulomatosis. *Hum Pathol.* 1972;3(4):457-558.

2. Pittaluga S, Wilson WH, Jaffe ES (eds). *World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon, UK: IARC Press; 2008.
3. Jaffe ES, Wilson WH. Lymphomatoid granulomatosis: pathogenesis, pathology and clinical implications. *Cancer Surv*. 1997;30:233–248.
4. Katzenstein AL, Carrington CB, Liebow AA. Lymphomatoid granulomatosis: a clinicopathologic study of 152 cases. *Cancer*. 1979;43(1):360–373.
5. Sordillo PP, Epremian B, Koziner B, Lacher M, Lieberman P. Lymphomatoid granulomatosis: an analysis of clinical and immunologic characteristics. *Cancer*. 1982;49(10):2070–2076.
6. Martin LK, Porcu P, Baiocchi RA, Erter JW, Chaudhury AR. Primary central nervous system lymphomatoid granulomatosis in a patient receiving azathioprine therapy. *Clin Adv Hematol Oncol*. 2009;7(1):65–68.
7. Kameda H, Okuyama A, Tamaru J, Itoyama S, Iizuka A, Takeuchi T. Lymphomatoid granulomatosis and diffuse alveolar damage associated with methotrexate therapy in a patient with rheumatoid arthritis. *Clin Rheumatol*. 2007;26(9):1585–1589.
8. Pereira AC, Oliveira TM, Nomelini RS, Saldanha JC, Calil MC, Murta EF. Lymphomatoid granulomatosis of the vulva: case report with immunohistochemical analysis. *J Obstet Gynaecol*. 2009;29(3):255–256.
9. Pisani RJ, DeRemee RA. Clinical implications of the histopathologic diagnosis of pulmonary lymphomatoid granulomatosis. *Mayo Clin Proc*. 1990;65(2):151–163.
10. Lee JS, Tudor R, Lynch DA. Lymphomatoid granulomatosis: radiologic features and pathologic correlations. *AJR Am J Roentgenol*. 2000;175(5):1335–1339.
11. McCloskey M, Catherwood M, McManus D, Todd G, Cuthbert R, Riley M. A case of lymphomatoid granulomatosis masquerading as a lung abscess. *Thorax*. 2004;59(9):818819.
12. Sehn LH, Donaldson J, Chhanabhai M, et al. Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia. *J Clin Oncol*. 2005;23(22):5027–5033.
13. Wilson WH, Kingma DW, Raffeld M, Wittes RE, Jaffe ES. Association of lymphomatoid granulomatosis with Epstein-Barr viral infection of B lymphocytes and response to interferon-alpha 2b. *Blood*. 1996;87(11):4531–4537.
14. Oren H, Irken G, Kargi A, et al. A pediatric case of lymphomatoid granulomatosis with onset after completion of chemotherapy for acute myeloid leukemia. *J Pediatr Hematol Oncol*. 2003;25(2):163–166.
15. Richter C, Schnabel A, Müller KM, Reuter M, Schuster P, Gross WL. [Lymphomatoid granulomatosis--remission induction with interferon-alpha 2b]. *Dtsch Med Wochenschr*. 1997;122(37):1106–1110. [Article in German]

Quiz: Pulmonary Lymphomatoid Granulomatosis Presenting with Neuropathy and Renal Nodules

EDUCATIONAL OBJECTIVES

1. To be able to describe the major clinical and laboratory features for a patient presenting with pulmonary lymphomatoid granulomatosis (PLG).
2. To be able to describe the pathologic features diagnostic of PLG.
3. To be able to describe the usual course and treatment for PLG.

PUBLICATION DATE: April 16, 2012

EXPIRATION DATE: April 16, 2013

QUESTIONS

1. Pulmonary lymphomatoid granulomatosis (PLG):
 - a. is a multi-organ systemic disease that usually affects the lungs with a lymphocytic invasion of vascular walls on biopsy
 - b. is generally considered a B-cell lymphoma.
 - c. has a benign, reactive T-cell component
 - d. a and b only
 - e. all of the above
2. Most cases of PLG:
 - a. are seen in patients with an underlying immunodeficiency disorder such as AIDS
 - b. are associated with malignant B-cells containing Epstein-Barr Virus RNA
 - c. have defects in cytotoxic T-cell function
 - d. a and b only
 - e. all of the above.
3. Clinical manifestations of PLG usually include:
 - a. lung nodules, often greater than 1 cm in diameter, in more than 90% of patients
 - b. skin involvement with patchy erythematous macules, papules, and plaques in about half the patients
 - c. early involvement of the liver and spleen in a majority of cases
 - d. a and b only
 - e. all of the above
4. Which of the following statements is false?
 - a. The definitive diagnosis of lymphomatoid granulomatosis on biopsy requires the presence of a polymorphic lymphocytic infiltrate, angitis due to transmural infiltrate of arteries and veins by lymphocytes, and granulomatosis with central necrosis within the lymphoid nodule.
 - b. Patients with PLG are treated as diffuse large B-cell lymphoma.
 - c. Most patients have a benign course with a 5-year survival of over 80%.
 - d. Patients under age 25, those with hepatosplenomegaly, and those with neurologic involvement had worse outcomes.
 - e. About 20% may achieve a clinical remission without treatment.

• • •

You may earn CME credit by reading the designated article in this issue and successfully completing the quiz (75% correct). Return completed quiz to *WMJ* CME, 330 E Lakeside St, Madison, WI 53715 or fax to 608.442.3802. You must include your name, address, telephone number, and e-mail address.

The Wisconsin Medical Society (Society) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The Wisconsin Medical Society designates this journal-based CME activity for a maximum of 1.0 *AMA PRA Category 1 Credit*[™]. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

advancing the art & science of medicine in the midwest

WMJ

WMJ (ISSN 1098-1861) is published through a collaboration between The Medical College of Wisconsin and The University of Wisconsin School of Medicine and Public Health. The mission of *WMJ* is to provide an opportunity to publish original research, case reports, review articles, and essays about current medical and public health issues.

© 2012 Board of Regents of the University of Wisconsin System and The Medical College of Wisconsin, Inc.

Visit www.wmjonline.org to learn more.