# Lymphomatoid Granulomatosis: A Diagnostic Challenge

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Lymphomatoid granulomatosis is a rare disease with close to 600 case reports in the literature to date. Just recently it was finally defined as an extranodal lymphoproliferative disease of uncertain malignant potential, consisting of Epstein-Barr virus-positive B cells, mixed with reactive T cells [1]. This ended a long debate about the nature of this rare and unclear entity, thought in the past to be of T cell origin. It mainly affects males aged 30–50 years, with a male to female ratio of at least 2:1 [1]. The disease has a circumstantial relation to past lymphoma, past chemotherapy, bone marrow transplantation, human immunodeficiency virus and EBV [ 2,3]. Presenting symptoms are fever, cough, dyspnea, malaise, weight loss, and dermatologic and neurologic manifestations. Some features of LG render the diagnosis elusive. Ninety percent of LG patients are symptomatic for 4–8 months prior to diagnosis [2]. The presenting symptoms listed above are suggestive of a neoplastic disease with a wide differential diagnosis related to infectious and autoimmune categories. Curiously, despite its lymphoproliferative nature, lymphatic tissue sites are not involved in LG, and multiple biopsies taken from lymph nodes, bone marrow and spleen do not contribute to the diagnosis [2]. These special features of LG are reflected in the unique clinical course of the patient described here.

## Patient Description

A 34 year old man was admitted because of prolonged low grade fever of 2 months duration, 12 kg weight loss and malaise. Two weeks before admission his temperature rose to 38.2–40°C daily, mostly during the evening. He was in good health prior to the onset of symptoms with no previous significant illness and no history of foreign travel.

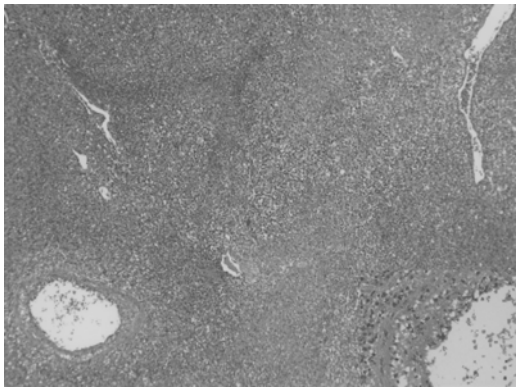
The only significant finding on physical examination was a markedly enlarged and non-tender spleen and pedal edema. Further evaluation disclosed white blood cells 2,000/mm$^3$, hemoglobin 10.5 g/dl, platelets 80,000/mm$^3$ and normal chemistry except for albumin 2.3 g/dl without proteinuria. Serologic workup for Brucella, Rickettsia, Mycoplasma, Q fever, cytomegalovirus, HIV, hepatitis B and C, Parvovirus, Leishmania, and thick blood smears for malaria, were negative. Positive serology for past infection with EBV was detected. Further workup, including C-reactive protein, rheumatoid factor, antinuclear factor, antineutrophil cytoplasmic antibodies, antiphospholipid antibodies, Coombs, complement 3 and 4, was normal. Haptoglobin was low (5.8, normal range 26–226).

Computerized tomography of the abdomen showed an enlarged spleen (23 cm) with few mesenteric lymph nodes. Chest CT revealed a small para-aortic lymph node measuring 7 mm with normal mediastinum and axillas. A lymph node biopsy and four bone marrow biopsies were normal. Explorative laparotomy and splenectomy did not disclose any pathology except for a markedly enlarged spleen. A thorough histologic examination of the entire spleen in multiple sections revealed congested splenic tissue with mild extramedullary hematopoiesis.

After the splenectomy the fever persisted with peaks reaching 41°C, however the leukopenia subsided slightly. The patient underwent a therapeutic trial of prednisone 80 mg/day, which resulted in disappearance of the fever, normalization of the WBC, gradual rise in albumin levels, amelioration of the severe edema, and improvement in his general condition.

About a month after the operation, while still on prednisone, the patient developed diffuse erythematous rash and livedo reticularis. This rash did not respond to corticosteroids or to methotrexate that was later added. Several skin biopsies disclosed reactive angioendotheliomatosis and vasculitis. The patient's blood counts showed a decrease: WBC 570/mm$^3$ (absolute neutrophils 230/mm$^3$), hemoglobin 7.3 g/dl and platelets 22,000/mm$^3$. Albumin was 2.3 g/dl, and pitting edema developed accompanied by severe right arm and lower limb pain that was later diagnosed as mononeuritis multiplex (electromyography and clinically based). A follow-up CT disclosed four small pulmonary nodules (7–10 mm) – two mediastinal and two in the lung parenchyma. Two of the pulmonary nodules had been recognized on a previous CT scan but were absent on a subsequent scan, reappearing on this scan. A diagnostic wedge lung biopsy was achieved by video-assisted thoracoscopy. Microscopic examination [Figure] demonstrated effacement of the lung architecture by aggregates of lymphoid cells of various sizes filling the alveolar spaces. Some of these lymphocytes were atypical, with prominent nucleoli. Plasma cells were

EBV = Epstein-Barr virus
LG = lymphomatoid granulomatosis
HIV = human immunodeficiency virus
WBC = white blood cells



Lung biopsy showing zonal necrosis and extensive lymphocytic infiltration obscuring the lung architecture (hematoxylin and eosin x 4). The inset demonstrates the intimate relation between a large blood vessel wall and lymphoid cells, many of them infiltrating the vessel wall (H&E x 40)

numerous in some of the aggregates. Extensive areas of necrosis and numerous apoptotic bodies were also present. Many of the lymphoid cells, especially the small ones, were tightly connected to the blood vessel walls, with infiltration of the walls, but no obvious vascular wall necrosis was demonstrated. Immunohistochemical stains confirmed the B lineage of most of the large and few of the small and medium lymphocytes, with lambda light chain restriction. Most of the lymphocytes were T cells (CD3 and CD43 positive), partly CD4 and partly CD8 positive. *In situ* hybridization for EBV was positive in all the large and some of the medium cells. These histologic and phenotypical features confirmed the diagnosis of EBV-related B cell angiocentric lymphoma, consistent with lymphomatoid granulomatosis grade 3.

Combined therapy with steroids and cyclophosphamide was started, with a good clinical response for 6 months. After this period clinical worsening in the disease course was observed with reappearance of high fever that required constant steroidal treatment. Autologous bone marrow transplantation was considered, but in the meanwhile the patient received combined chemotherapy according to the CHOP protocol along with monoclonal anti-CD20 antibody (Mabtera) with no satisfactory clinical results. He had high fever and persistent purulent sinusitis requiring surgical drainage along with antibiotic therapy. One month later the patient expired with a clinical picture of fulminant sepsis without laboratory evidence of systemic or localized infection

## Comment

The clinical course in this patient and the prolonged diagnostic workup before a diagnosis was reached demonstrate the difficulty in diagnosing LG. Although typical of this rare entity, the diagnostic workup took 9 months and the clinical course after the diagnosis lasted a similar period, eventually with no benefit. The rarity of LG, combined with the absence of lymphoid tissue involvement, despite its lymphoproliferative nature, render the diagnosis elusive. In addition, the tendency of pulmonary nodules to wax and wane, as occurred in the clinical course described above, might affect the decision to take a pulmonary biopsy. Evidently, this biopsy was necessary to achieve a histologic diagnosis. LG should be suspected in patients presenting with clinical features suggestive of a lymphoproliferative disorder with normal lymphatic tissue and marked extra-lymphatic involvement.

LG, also known as angiocentric immunoproliferative lesion, is an angiocentric and angiodestructive lymphoproliferative disease involving EBV-positive neoplastic B cells, a prominent inflammatory background, and marked vascular changes. LG is considered to be one of the lymphoproliferative disorders causally related to EBV infection. Viral proteins such as EBV nuclear antigen and LMP (latent membrane proteins) and genomic sequences of EBV are found in involved lymphoid tissue among 60–70% of LG patients [2]. Whether EBV causes insertional mutagenesis leading to a lymphoproliferative disorder or reflects an immunodeficiency has yet to be investigated.

The disease has a spectrum of histologic grade and clinical aggressiveness that is related to the proportion of the large B cells. Demonstration by *in situ* hybridization of 0–4 and 5–20 cells positive for EBV per high power field corresponds with grade 1 and 2, respectively. Grade 3 is an overt large cell lymphoma that could be considered a type of T cell-rich large B cell lymphoma [1]. Morphologically, LG enters the differential diagnosis of pulmonary lymphoid lesions and also of angiocentric lesions [4]. The disease is mainly extranodal, with the lung being most frequently involved. Lymph nodes and spleen are very rarely involved [1]. Our patient had pancytopenia and marked splenomegaly that necessitated splenectomy. Although the disease course was typical for LG, the diagnosis remained elusive until the final proof provided by the lung biopsy. Detailed histopathologic examination of the spleen did not reveal involvement of the spleen by lymphoma, and the cause of the splenomegaly remains unclear.

Based on combined clinical and pathologic features, the main differential diagnosis should be suspected in patients with lymphoid and angiocentric pulmonary lesions. Our patient was diagnosed as LG grade 3. The therapeutic options available at present are limited. Autologous bone marrow transplantation was considered, based on a single report in the literature, but eventually was not applied in our patient [5]. Additional therapeutic options, including early bone marrow transplantation, are yet to be further investigated.

## References


1. Jaffe ES, Wilson WH. Lymphomatoid granulomatosis. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, eds. World Health Organization Classification of Tumors. Pathology and Genetics of Haematopoietic and Lymphoid Tissues. Lyon: IARC Press, 2001:185–7.
2. Cadranel J, Wislez M, Antoine M. Primary pulmonary lymphoma. *Eur Respir J* 2002;20: 750–62.
3. Myers JL, Kurtin PJ, Katzenstein AL. Lymphomatoid granulomatosis. Evidence of immunophenotypic diversity and relationship to Epstein-Barr virus infection. *Am J Surg Pathol* 1995;19(11)1300–12.
4. Patchefsky AS. Nonneoplastic pulmonary disease. In: Mills SE, Carter D, Greenson JK, Oberman HA, Reuter V, Stoler MH, eds. Sternberg's Diagnostic Surgical Pathology. 4th edn. Philadelphia: Lippincott Williams & Wilkins, 2004:1133–40.
5. Bernstein ML, Reece ER, de Chadarevian JP. Bone marrow transplantation in lymphomatoid granulomatosis. Report of a case. *Cancer* 1986;58(4):969–72.



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