

Lymphomatoid Granulomatosis: A Rare Mimicker of Vasculitis

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ABSTRACT. Lymphomatoid granulomatosis (LG) is a rare Epstein-Barr virus-associated lymphoproliferative disorder, with a propensity for blood vessel destruction. Although it most commonly affects the lung, it can affect multiple extrapulmonary sites (i.e., skin, nervous system, gastrointestinal tract, liver, spleen, kidney, and heart). Since LG often mimics systemic vasculitis, it presents a diagnostic clinical challenge. We describe a case of LG with no pulmonary involvement, which was thought to be systemic vasculitis on the basis of multiorgan involvement and biopsy findings. (*J Rheumatol* 2005;32:2242–5)

Key Indexing Terms:

LYMPHOMATOID GRANULOMATOSIS
POLYARTERITIS NODOSA

LYMPHOMA

WEGENER'S GRANULOMATOSIS
SYSTEMIC VASCULITIS

Lymphomatoid granulomatosis (LG) is a rare Epstein-Barr virus (EBV) associated B cell lymphoproliferative disorder with the propensity for angiocentric or blood vessel destruction. It most commonly affects the lung, but can also involve multiple extrapulmonary sites. Because of its tendency for multiorgan involvement and histological features suggestive of angitis, LG often mimics systemic vasculitis and can present as a diagnostic challenge for clinicians.

CASE REPORT

A 62-year-old Hispanic man was admitted to Olive View–UCLA Medical Center (OVMC) in July 2003 with a one-year history of progressive upper and lower extremity weakness, purpura, and burning pain in the legs. His antinuclear antibody (ANA; titer: 1:160) and rheumatoid factor (1:32) were positive, but his antineutrophil cytoplasmic antibody (ANCA) was negative. Abdominal angiogram showed normal celiac and mesenteric arteries. On clinical grounds, a rheumatologist diagnosed him as having acute to subacute ascending sensory-motor polyneuropathy secondary to vasculitis. He was treated with cyclophosphamide and high dose corticosteroids from February to June 2003.

Review of systems was significant for malaise, anorexia, migratory arthralgias, and 60 lb weight loss. On physical examination, he was afebrile with normal vital signs and markedly cachectic. Large erythematous-purple

plaque-like skin lesions were noted over both shins. Neurological examination showed bilateral muscle atrophy of the upper and lower extremities, (distal greater than proximal motor weakness), sensory abnormality of painful dysesthesia in the lower extremities, and absent reflexes in the lower extremities and distal upper extremities. Normal or negative initial laboratory investigations included white blood cell count (WBC, 4000/mm³), creatinine (0.5 mg/dl), creatine kinase (< 20 mg/dl), HIV serology, hepatitis B and C serologies, cryoglobulins, rapid plasma reagin, and repeat measure of ANA and ANCA. Abnormal laboratory investigations included: low hemoglobin (8.9 g/dl) and high Westergren erythrocyte sedimentation rate (74 mm/h). Differential diagnoses included vasculitis, malignancy, or infection.

Further laboratory testing revealed a monoclonal gammopathy of unknown significance on serum protein electrophoresis, while urine protein electrophoresis was normal. A radiographic skeletal survey was negative for lytic bone lesions. A skin lesion punch biopsy (Figure 1A) showed mild superficial perivascular dermatitis and single small-artery occlusive vasculopathy, nondiagnostic for vasculitis. Muscle and sural nerve biopsy showed marked ischemic-appearing muscle fiber degeneration and focal severe perivascular and intramural lymphocytic inflammation of small vessels, consistent with ischemic muscle damage due to a focal chronic severe vasculitis (Figure 1B). Two weeks later, he was discharged, with a presumed diagnosis of a sensory-motor polyneuropathy due to vasculitis, based on the muscle and nerve biopsy. He was treated with prednisone 30 mg/day and low dose oral daily cyclophosphamide (75 mg/day).

At one-month followup, his plaque-like purpuric skin lesions and burning pain in his lower extremities had improved, but he continued to have marked generalized weakness. In September 2003, he presented to OVMC Emergency Room with acute abdominal pain, nausea, vomiting, and diarrhea. His temperature was 40°C, pulse 137/min, blood pressure 116/76 mm Hg, and respiratory rate 26/min. His abdomen was distended and he had rebound tenderness. Laboratory studies showed pancytopenia (WBC 1000/mm³, hemoglobin 7.5 g/dl, and platelet count 36,000/mm³). A panel of metabolic tests showed an elevated anion gap (18 mmol/l with low bicarbonate of 13 mmol/l). Abdominal plain radiographs showed markedly distended bowel loops without free air. He started intravenous (IV) antibiotics for sepsis, was intubated, and was admitted to the intensive care unit (ICU). The surgical team performed an emergent exploratory laparotomy for acute abdomen. Intraoperatively no bowel perforation or other significant

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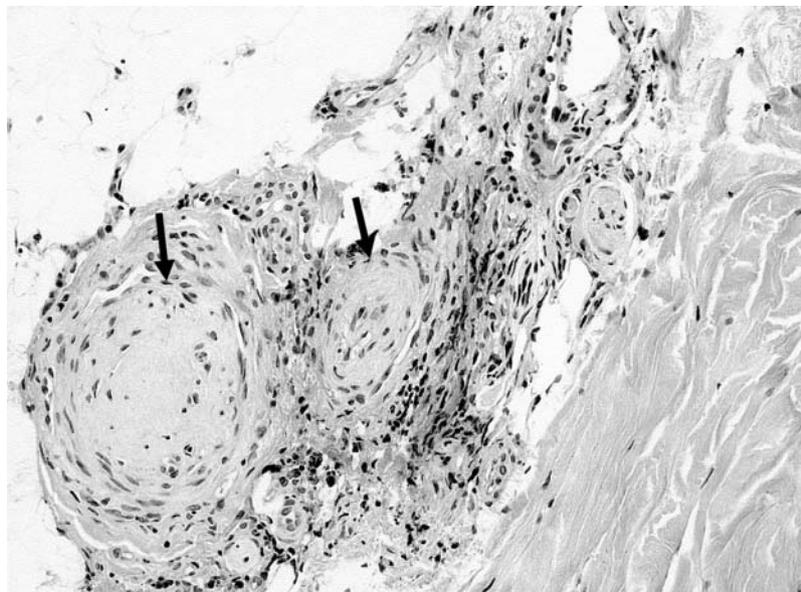


Figure 1A. Skin biopsy of lower leg: occlusive vasculopathy of small artery (arrows).

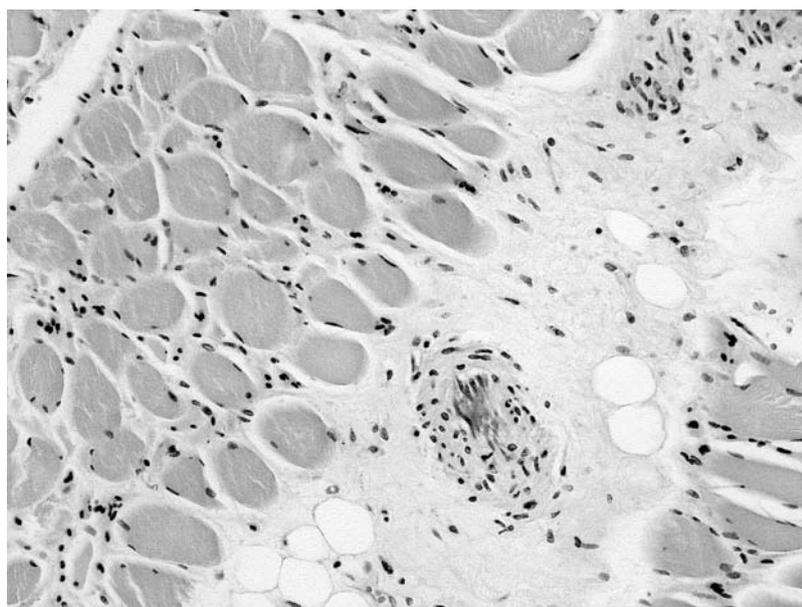


Figure 1B. Lymphocytic vasculitis. Arteriolar intramural infiltration by small lymphocytes. H&E, original magnification $\times 100$.

pathologies were found except for a small amount of ascites in the peritoneal cavity. Intraoperative biopsies were not performed.

The next day, he developed gastrointestinal (GI) bleeding, but no endoscopy was performed. He was treated empirically with IV lansoprazole. Abdominal and pelvic computerized tomographic scan (obtained on ICU Day 2) showed bilateral pleural effusions, ascites, and splenomegaly, with 2 hypodense lesions in the spleen that were consistent with infarction (Figure 2A); no intraabdominal lymphadenopathy was reported at the time. At this point, differential diagnoses of acute deterioration included overwhelming infection, bowel ischemia secondary to abdominal vasculitis, and/or malignancy infiltration. Blood, urine, and sputum cultures were negative. A peripheral blood smear, however, now showed atypical lymphocytes and smudge cells, highly suspicious for hematological malignancy. Bone marrow biopsy was consistent with reactive process (such as to EBV,

cytomegalovirus, or toxoplasmosis), or possibly even a treated chronic lymphocytic leukemia. On ICU Day 14, he became acutely hypotensive, had profuse GI bleeding, and expired after an unsuccessful resuscitation.

Autopsy findings. The cause of death was multiorgan failure: GI hemorrhage from ischemic enteritis, diffuse alveolar damage, bronchopneumonia with cytomegalovirus and fungal infection, and renal failure. Enlargement of paraaortic, mesenteric, and omental lymph nodes was striking, consistent with malignant lymphoma. Postmortem review of the earlier abdominal CT scan did show extensive intraabdominal lymphadenopathy (Figure 2B). The bone marrow, spleen, stomach, small intestine, and mesentery also showed malignant lymphoma (Figure 3). By in situ hybridization, EBV-positive cells were extremely numerous. The final diagnosis was a B cell lymphoma, which was EBV-positive, with features most consistent with lymphomatoid granulomatosis-like (or angiocentric immunoproliferative) lymphoma.



Figure 2A. CT of the abdomen shows splenomegaly with splenic infarcts (arrows).



Figure 2B. CT of the abdomen shows diffuse mesenteric and paraaortic lymphadenopathy (arrows).



Figure 3. Malignant lymphoma involving mesentery; multiple 1.5–2 cm nodules are visible.

DISCUSSION

Lymphomatoid granulomatosis is a rare angiocentric and angiodestructive lymphoproliferative disorder associated with the malignant transformation of B lymphocytes by EBV^{1,2}. LG is characterized by lymphocytic vasculitis with infiltration of the vessel wall by a mixture of reactive and atypical cells that may lead to necrosis¹. The diagnosis hinges upon detecting EBV-positive B cells³. Although the lung is affected most frequently, LG also affects other organs. Because of its propensity for multiorgan involvement and the histological features of angiitis, LG often mimics systemic vasculitis, most notably Wegener's granulomatosis (WG). Clinical similarities between LG and WG usually include the presence of lung nodules, renal dysfunction, and a polymorphic inflammatory infiltrate associated

with necrosis¹. In the present case, however, pulmonary and renal involvement were lacking. Nonreactive ANCA coupled with diffuse arthralgias, skin lesions, peripheral polyneuropathy, and GI involvement suggested polyarteritis nodosa (PAN).

The difficulty in achieving a definitive diagnosis in our patient, even with skin, nerve, muscle, and bone marrow biopsies, illustrates several challenges of detecting LG in its early stages, particularly in the absence of typical pulmonary lesions. First, since there are few EBV-infected B cells in skin, histological examination of cutaneous/subcutaneous tissue is rarely diagnostic of LG³. Second, low-grade LG lesions may be difficult to distinguish from vasculitis histologically. For example, grade I lesions contain a polymorphous lymphoid infiltrate in vessel walls, with rare cytologic atypia or EBV-positive cells⁴. Finally, easily accessible biopsy sites such as lymph nodes and bone marrow are not usually involved early in the disease³.

Because the treatment and prognosis are different, differentiating LG from the vasculitides (WG, PAN) is essential. While corticosteroid and cytotoxic agents are commonly lifesaving for the vasculitides⁵, the therapeutic approach for LG is not as successful. In early series, LG was usually progressive, fatal, and poorly responsive to treatment despite some reports of spontaneous remission^{1,6}. Treatment includes corticosteroid and/or cyclophosphamide, interferon- α , or — depending on the histological grade — combination chemotherapy⁶⁻⁸. New therapeutic approaches to LG (rituximab and autologous hematopoietic stem cell transplant^{9,10}) have also been reported to achieve complete disease remission.

According to Jaffe, *et al*, the histological grade of LG may progress over time or differ from site to site³. One strat-

egy for increasing the yield of biopsy might be to perform repeat biopsies as the disease progresses or to obtain biopsies from different sites. This strategy should be seriously considered in cases where vasculitis is suggested but the diagnosis is in question, and the patient is not responding clinically.

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