An 18-Year-Old Man With Persistent Cough and Bilateral Lower Lung Infiltration

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An 18-year-old Hispanic man initially presented with fever and cough in April 2004. His chest radiograph showed bilateral pulmonary infiltrates and he was treated with azithromycin. His fever was resolved but a dry cough persisted. He also complained of fatigue but denied hemoptysis, chest pain, or other symptoms. Ciprofloxacin was administered and his symptoms were slightly improved. Repeat chest radiograph showed no change of the infiltrate after antibiotic treatment. His temperature was 99.3°F (37.4°C); blood pressure, 101/65 mm Hg; hemoglobin, 12.9 g/dL; red blood cells, 4.5 × 10⁶/L; white blood cells, 7.9 × 10³/µL; sodium, 134 mEq/L; potassium, 4.4 mEq/L; calcium, 7.9 mg/dL; magnesium, 1.6 mEq/L; and O₂ saturation, 97%. His erythrocyte sedimentation rate was 1 mm/h. Serology tests for antineutrophil cytoplasmic antibody, angiotension-converting enzyme, antinuclear antibody, and rheumatoid factor all had negative results. Because of cough, fatigue, and persistent shortness of breath, a bronchoscopy was performed. No malignant cells were detected; an acid-fast bacteria culture had negative results. There were also negative results for tests for human immunodeficiency virus, Aspergillus, Microspora, Candida, Pneumocytis carinii, and Thermoactinomyces vulgaris. A hypersensitivity pneumonitis panel also had negative results.

Several chest computerized tomographic scans during a period of 2 months revealed progressively worsening diffuse alveolar infiltration. In addition, a 2.5 cm left lower lobe cavitary mass was subsequently detected; therefore, an open lung biopsy was performed. During the procedure, 300 mL of pleural effusion was collected. The pleura and pericardium were hyperemic. The left lower lobe of the lung was nearly completely consolidated with fibrous exudates at the base, which made the lung friable. A large lymph node was palpated within the inferior pulmonary ligament. The node was excised and sent to the laboratory for pathologic examination, along with a wedge biopsy of the left lower lobe and 1 lymph node that was detected in the lingula of the left upper lobe.

Both lung and lymph node showed a diffuse or nodular lymphohistiocytic infiltrative process, characterized by a spectrum of lymphoid cells ranging from small and mature to atypical large, admixed with epithelioid histiocytes. Plasma cells were abundant in the lymph node and around the lymphohistiocytic infiltrate in the pleura, where they formed sheets and were associated with edema and pleural exudates. The lung parenchyma showed fibrosis with honeycomb change. The architecture of the lymph node was completely obliterated by the proliferation of small and atypical large lymphoid cells (Figure 1, A).

The infiltrate involved the vessel wall, forming necrosis (Figure 1, B) and atypical granulomas (Figure 2). Immunohistochemistry stain revealed that small proliferative lymphocytes were CD3⁺ T cells, and atypical plasmacytoid cells were largely CD79a⁺ and CD38⁺ but CD20⁻. The medium- to large-sized atypical lymphoid cells were CD10⁻ and CD20⁺ cells (Figure 3). In situ hybridization for Epstein-Barr early RNA (EBER) had positive results in both lung and lymph node (Figure 4). The CD20⁺ B-cell population showed a light-chain restriction by immunohistochemistry. The immunoglobulin H gene arrangement study by polymerase chain reaction showed a monoclonal proliferation of B cells with a distinctive band around 100 kb. The T-cell population was polyclonal. Epithelioid histiocytes were stained positive for CD68. Staining for CD15 and CD30 was negative.

What is your diagnosis?
Pathologic Diagnosis: Epstein-Barr Virus–Positive Lymphoproliferative Disorder Consistent With Lymphomatoid Granulomatosis

Abstract

An 18-year-old man presented with low-grade fever and dry cough with bilateral lower lobe infiltrates that did not respond to antibiotic treatment. The open lung biopsy showed a nodular lymphohistiocytic proliferative process. Lymphocytes were small to medium in size and admixed with atypical large lymphocytes and plasmacytoid cells that infiltrated both lung and lymph nodes and formed angiocentric necrosis. Histiocytes that were positive for CD68 were abundant. Atypical lymphocytes were positive for CD20, negative for CD10, and showed light-chain restriction. The polymerase chain reaction immunoglobulin H gene rearrangement study showed monoclonal B-cell proliferation. Those B cells were strongly positive for Epstein-Barr early RNA in the in situ hybridization.

Lymphomatoid granulomatosis (LYG) was first described in 1972. The average age of occurrence is in the 50s. It is uncommon in people younger than 20 years. By World Health Organization definition, LYG is defined as an angiocentric and angiodestructive lymphoproliferative disease involving extranodal sites, composed of B cells positive for Epstein-Barr virus (EBV) and admixed with reactive T cells. The most common site of involvement is the lung. Other common sites of involvement include brain, kidney, liver, and skin. Morphologically, 3 grades are recognized: grade I, II, and III. Grade III LYG should be approached clinically as a subtype of diffuse large B-cell lymphoma. The angiocentric and angiodestructive lymphoreticular proliferation is a unique feature, which is not seen in other types of lymphomas. The lymph nodes, spleen, and bone marrow usually are spared until the late stage of illness. Grade I lesions have a polymorphous angiocentric infiltrate without conspicuous lymphocyte atypia and with minimal-to-absent necrosis. The number of EBV+ cells were either fewer than 5 per high-power field or absent. Grade II lesions have angioinvasion and/or angiodestruction. The lesion has scattered large or hyperchromatic lymphoid cells with fewer than 20 EBV+ cells per high-power field. Necrosis is almost always present but is not extensive. Grade III lesions contain large atypical lymphoid cells in a polymorphous background; the number of EBV+ cells is more than 20 per high-power field. Confluent necrosis is often present.

The pulmonary involvement characteristically shows nodules or masses (80%–90%) with ill-defined margins. Those nodules range from 5 to more than 60, with most being smaller than 1 cm. Twenty percent of the nodules have reticulonodular infiltrates and 30% show cavity formation caused by coagulative necrosis. Both pulmonary vein and arteries can be involved by the disease process with vasculitis-like changes.

The characteristic histologic features of LYG are the triad of polymorphic lymphoid infiltrate, angitis, and granulomatosis. Granulomas in LYG usually are atypical. They do not have typical multinucleated giant cells. They are composed of either polyclonally or clonally proliferating, small-to-medium (rarely large), atypical B cells admixed with a background of histiocytes, plasma cells, and reactive T cells. Angiodestructive necrosis can be present, as seen in the case presented here. The B cells that are infected with the EBV are seen in 50% to 70% of cases.

It seems that occurrence of LYG is associated with immunosuppressive conditions. There are many well-documented cases in which cutaneous or systemic LYG has been encountered in individuals with Wiskott-Aldrich syndrome, X-linked lymphoproliferative disorder, common variable immunodeficiency, severe hypogammaglobulinaemia, postautologous stem cell transplantation, following heart-lung transplantation, poststatus renal transplant, or after completion of chemotherapy for acute myeloid leukemia or acute lymphoblastic leukemia, as well as in patients with acquired immunodeficiency syndrome.

The progression of LYG to high-grade B-cell lymphoma occurs in 12% to 47% of cases, especially those cases without complete remission after treatment that almost inevitably evolve into lymphoma. The mortality rate ranges from 53% to 64%. Interferon alfa-2b as an effective form of therapy has been developed in recent years. Lately, rituximab monotherapy has been reported to achieve complete remission of LYG.

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References

4. World Health Organization Classification of Tumours; vol 10.