Residents' Clinic

39-Year-Old Man With Fever, Cough, and Dyspnea

ELIZABETH M. KANG, M.D.*, SYED W. MALIK, M.D.,† AND PAUL D. SCANLON, M.D.‡

A 39-year-old man requested a medical consultation from his hometown physician because of a 1-week history of dyspnea on exertion, fatigue, and a productive cough, which began after a trip to New Mexico. He received an orally administered cephalosporin antibiotic for 6 days for presumptive treatment of “bronchitis.” Subsequently, however, high fevers (to 39.4°C) and night sweats developed. The patient was admitted to a local hospital because of worsening dyspnea and fever. Findings on review of systems were otherwise unremarkable. He was a competitive athlete and had no major past medical illnesses and no family history of significant disease. He denied having risk factors for acquired immunodeficiency syndrome (AIDS). The arterial carbon dioxide tension of 50 and 34 mm Hg, respectively, and oxygen saturation of 87%. A chest roentgenogram revealed diffuse bilateral interstitial alveolar infiltrates with sparing of the lung bases. Gram’s stain of a sputum specimen showed no organisms.

1. At this point, which one of the following measures is least appropriate in the management of this patient?
   a. Administration of antibiotics to cover organisms for community-acquired pneumonia
   b. Sputum cultures for bacteria and fungi
   c. Direct fluorescent antibody test of sputum for Legionella
   d. Mycoplasma, Legionella, and viral serologic tests
   e. Addition of prednisone to treatment regimen along with antibiotics

   At this point, the most likely explanation for this patient’s symptoms is an infectious pneumonia. The potential etiologic organisms for a community-acquired pneumonia in a relatively young patient with no comorbid illness include Streptococcus pneumoniae, M. pneumoniae, Legionella species, Chlamydia pneumoniae, and viruses such as influenza A. Bacterial and fungal cultures as well as serologic tests for viruses (cytomegalovirus, Epstein-Barr virus, and influenza), Mycoplasma, and Legionella species are appropriate because the patient has not responded to conventional therapy for community-acquired pneumonia. His travel history suggests a possible exposure to Hantavirus, as New Mexico is the geographic area where Hantavirus pulmonary syndrome was first described. Nevertheless, the prolonged course of his illness does not resemble this syndrome, which is characterized by respiratory failure within a few days after the onset of symptoms. Coccidioidomycosis, which is also endemic to New Mexico, could likewise be considered. Fungal serologic tests were negative. Corticosteroids have a beneficial effect on the outcome in moderate to severe Pneumocystis carinii pneumonia in patients with AIDS, and the corticosteroid treatment should be started early in the course of the illness. In our patient, however, initial assessment did not suggest an immunocompromised state or AIDS. Beginning corticosteroid therapy in the presence of a possible active infection may adversely influence the outcome and thus is inappropriate.

During his initial hospitalization, the patient was treated empirically with intravenously administered erythromycin and ampicillin-sulbactam for presumed community-acquired pneumonia. Bacterial and fungal cultures of sputum and blood specimens were negative. Sputum smears showed no acid-fast organisms. A direct fluorescent antibody test and a serologic test for Legionella, as well as a mononucleosis spot slide test, were negative. Epstein-Barr virus IgG antibody was positive, and the cold agglutinin titer was 1:112. Bronchoalveolar lavage was performed, but the stains and cultures of lavage fluid for bacteria, viruses, fungi, and mycobacteria failed to identify an organism. Because of lack of improvement, the antibiotic regimen was changed to doxycycline, ganciclovir, and ciprofloxacin; the presumed diagnosis was viral pneumonia complicated by bacterial superinfection. The dyspnea diminished somewhat, and he was dismissed from the hospital with home oxygen administered by nasal cannula and intravenously and orally administered antibiotics.

Within 72 hours after hospital dismissal, the shortness of breath, cough, and fever progressed. The patient was then transferred to our institution and admitted to the medical intensive-care unit.

*Resident in Internal Medicine, Mayo Graduate School of Medicine, Mayo Clinic Rochester, Rochester, Minnesota.
†Fellow in Pulmonary and Critical Care Medicine, Mayo Graduate School of Medicine, Mayo Clinic Rochester, Rochester, Minnesota.
‡Adviser to resident and fellow and Consultant in Pulmonary and Critical Care Medicine, Mayo Clinic Rochester, Rochester, Minnesota.

See end of article for correct answers to questions.

Address reprint requests to Dr. P. D. Scanlon, Division of Pulmonary and Critical Care Medicine, Mayo Clinic Rochester, 200 First Street SW, Rochester, MN 55905.

On physical examination, a slim, athletic-appearing man was noted to be in moderate respiratory distress but alert and oriented. He had a respiratory rate of 36 breaths/min, heart rate of 110 beats/min, blood pressure of 130/80 mm Hg, and temperature of 38°C. Inspiratory crackles were heard over both lungs. With a fractional concentration of oxygen in inspired gas of 1.0 with use of a nonrebreathing mask, the arterial oxygen and carbon dioxide tensions were 61 and 31 mm Hg, respectively, and the pH was 7.49. The leukocyte count was 6.5 x 10^9/L, hemoglobin concentration was 12.7 g/dL, and platelet count was 122 x 10^9/L. The blood chemistry analysis showed a creatinine of 1.1 mg/dL, total bilirubin of 0.9 mg/dL, alkaline phosphatase of 290 U/L, and aspartate aminotransferase of 106 U/L. A chest roentgenogram (Fig. 1) showed bilateral peripheral alveolar infiltrates with sparing of perihilar and basal lung zones.

2. Which one of the following disease entities is most likely to cause the chest roentgenographic abnormality detected in our patient (Fig. 1)?
   a. Cardiogenic pulmonary edema
   b. Adult respiratory distress syndrome (ARDS)
   c. Idiopathic bronchiolitis obliterans organizing pneumonia (BOOP)
   d. Chronic eosinophilic pneumonia (CEP)
   e. Idiopathic pulmonary fibrosis

   Our patient’s chest roentgenographic abnormality was reported to demonstrate a pattern of “reverse pulmonary edema.” This characteristic abnormality resembles the photographic negative of cardiogenic pulmonary edema, which typically begins with congestion around the hilum. ARDS is characterized by diffuse alveolar infiltrates due to the leakage of capillaries throughout the lungs. BOOP is also called cryptogenic organizing pneumonia. Patients with BOOP are usually middle-aged and have a “flulike” illness with cough, fever, malaise, and weight loss. Lung biopsy specimens reveal polypoid masses of granulation tissue in lumens of small airways, alveolar ducts, and some alveoli. The most common radiographic pattern is bilateral patchy airspace opacities with a “ground glass” appearance. Although a peripheral distribution of infiltrates with the reverse pulmonary edema pattern can be seen in idiopathic BOOP, this finding is considered a fairly typical sign of CEP. The latter most commonly occurs in women, unlike BOOP, which affects both genders equally. CEP also manifests with systemic symptoms, including fevers, malaise, night sweats, a productive cough, and wheezing. It is often associated with an eosinophilia in both blood and bronchoalveolar lavage fluid and has a good response to oral corticosteroid therapy. CEP may recur when the dose of corticosteroids is tapered, and patients may require long-term therapy. Idiopathic pulmonary fibrosis is characterized by a bilateral lower zone predominance of reticulonodular infiltrates, “honeycomb” lungs, lower lobe contraction, and additional diffuse infiltrates with perihilar distribution.

Because of progressive respiratory distress, the patient required tracheal intubation and mechanical ventilation within 24 hours after admission. Cultures of fluid from bronchoalveolar lavage performed at the local hospital remained negative. The patient’s respiratory status continued to deteriorate.

3. Which one of the following diagnostic interventions would be most appropriate in the management of this patient at this time?
   a. Continuation of antibiotic therapy pending results of cultures
   b. Reperformance of bronchoalveolar lavage
   c. Bronchoscopic lung biopsy
   d. High-resolution computed tomography (HRCT) of the chest
   e. Open-lung biopsy

   Despite administration of several antibiotics, the respiratory status of the patient continued to deteriorate progressively until mechanical ventilatory support was necessary. A more definitive diagnostic intervention was urgently needed. Repeating the bronchoalveolar lavage was unlikely to provide additional diagnostic information after noncontributory results of an earlier procedure. Bronchoscopic lung biopsy is not as safe as open-lung biopsy in patients who require mechanical ventilation. HRCT of the lungs offers better resolution of parenchymal abnormalities in comparison with chest roentgenography and conventional computed
If one assumes that the primary pathologic process is thorotomography (CT). It is useful in the diagnosis of certain interstitial lung diseases, such as eosinophilic granuloma, lymphangioleiomyomatosis, and lymphangitic carcinomatosis, and may even eliminate the need for open-lung biopsy. Some clinicians advocate its use in the diagnosis of idiopathic pulmonary fibrosis. HRCT, however, does not exclude infection and would be unlikely to establish a definitive diagnosis in the current case. Open-lung biopsy, despite being invasive, has a high diagnostic yield, a matter of utmost importance in this patient.

An open-lung biopsy, performed the following morning, revealed a diffuse T-cell lymphoma of the lung. The cells were large, cytologically atypical, and immunoreactive for CD3 and CD45RO (UCHL-1).

4. If one assumes that the primary pathologic process is limited to this patient's lungs only, which one of the following statements is not true?
   a. Primary lymphomas of the lungs are very uncommon
   b. Usually, open-lung biopsy is necessary for diagnosis
   c. Primary non-Hodgkin's lymphoma in the lung is more common than Hodgkin's disease
   d. Most primary lymphomas in the lung are of T-cell lineage
   e. The prognosis of patients with B-cell-derived lung lymphomas is relatively favorable in comparison with that associated with T-cell lymphomas

Primary malignant lymphomas of the lung are rare. For diagnosing primary pulmonary lymphoma, the patient must have no evidence of extrathoracic disease, no mediastinal node involvement, and no prior history of lymphoma. Primary lymphoma of the lung still necessitates lung biopsy—either by a transthoracoscopic procedure or by open thoracotomy—for diagnosis, although new immunologic markers may facilitate diagnosis in the future. Primary non-Hodgkin's lymphoma of the lung is more common than Hodgkin's disease, and most such tumors demonstrate evidence of B-cell lineage. In a series of 62 primary malignant lymphomas described by Li and colleagues, 58 were of B-cell and only 2 were of T-cell type (2 others were not characterized). The prognosis of patients who had B-cell-derived lung lymphomas without constitutional symptoms was relatively favorable (5-year survival, 60 to 84%) regardless of whether the tumors had low- or high-grade histologic features. In contrast, patients with constitutional symptoms and those with T-cell lymphomas had a poor outcome. Both patients with T-cell lymphoma died within 6 months after diagnosis.

Our patient underwent staging evaluations that included bone marrow biopsy and CT of the abdomen. These tests revealed lymphomatous involvement of the bone marrow and enlarged para-aortic lymph nodes, consistent with stage IVB lymphoma of the lungs. Thus, his disease could not be categorized as a primary pulmonary lymphoma; rather, he had generalized lymphoma with preponderant respiratory manifestations.

5. Epstein-Barr virus, detected earlier in our patient, is unlikely to be implicated in which one of the following neoplastic disorders?
   a. Burkitt's lymphoma
   b. T-cell lymphoma
   c. Lymphomatoid granulomatosis
   d. Posttransplantation lymphoproliferative disorders
   e. Carcinoid tumors of the lung

Epstein-Barr virus causes infectious mononucleosis and has also been linked to several tumors, presumably by its ability to incorporate itself into the host cell genome and immortalizing B-cell lines. The first association was discovered by culturing lymphoblasts from patients with Burkitt's lymphoma. Epstein-Barr virus genome has also been found in some T-cell lymphomas, and Epstein-Barr virus antibodies have been detected in patients with T-cell lymphomas. Lymphomatoid granulomatosis is a lymphoproliferative disorder with distinctive pulmonary lesions that contain a polymorphous and atypical lymphoreticular infiltrate, a striking vasculitis, and variable necrosis. Posttransplantation lymphoproliferative disorders are thought to result from immunosuppressive therapy, which renders T-cell populations inadequate or ineffective to respond to proliferation of B cells induced by Epstein-Barr virus. The frequency depends on the type of transplantation and the amount of immunosuppression needed. Both lymphomatoid granulomatosis and posttransplantation lymphoproliferative disorders have been associated with Epstein-Barr virus, but carcinoid tumors have not.

The patient received two cycles of high-dose combination chemotherapy that consisted of cyclophosphamide, doxorubicin, vincristine sulfate, and prednisone. Neutropenia and fever developed, and he was initially treated empirically with ceftazidime and vancomycin; because of persistent fever, amphotericin B was subsequently added. No infectious organism was identified. A CT scan of the chest obtained 5 weeks after initiation of therapy showed a right upper lobe cavitary mass, but cultures of both bronchoalveolar lavage fluid and bone marrow were negative. Six weeks after receiving the first cycle of chemotherapy, the patient became jaundiced and had increased liver enzymes and bilirubin. Liver biopsy showed lymphomatous involvement. Although one cycle of cisplatin-based chemotherapy was administered, progressive dyspnea and hypoxemia developed. He declined further therapy and died 1 week later (approximately 13 weeks after the initial onset of symptoms).
DISCUSSION
This patient initially had a febrile respiratory illness and was treated for a presumed community-acquired pneumonia. Because no improvement ensued despite adequate antibiotic therapy, other diffuse interstitial lung disorders, including atypical viral and fungal pneumonias and neoplastic conditions, were considered. A chest roentgenogram showed the classic pattern of CEP—reverse pulmonary edema. Another consideration was acute lung injury or ARDS in response to an undefined initial insult (for example, a viral pneumonia). ARDS can occur as a result of such insults as toxic inhalation, sepsis, or pancreatitis. The clinical course is often long and complicated, and related mortality is 40 to 80% from respiratory failure, sepsis, or multiorgan failure. The characteristic initial pathologic findings are exudative edema and hyaline membranes due to the leakage of proteinaceous fluid into the airspace from endothelial injury. Subsequently, a mononuclear cell proliferative stage is followed by a fibrotic stage.

Non-Hodgkin’s lymphomas are conventionally classified as low-grade, intermediate-grade, and high-grade varieties. The low-grade lymphomas have a long natural history with an indolent course, and patients often have advanced disseminated disease at the time of diagnosis. Because of delayed diagnosis, low-grade lymphomas often are associated with a poor outcome and do not respond favorably to chemotherapy. Treatment options range from careful observation to palliative chemotherapy. High-grade lymphomas often occur in unusual sites and progress rapidly. Because of occult involvement of the central nervous system, intrathecal administration of chemotherapy is frequently used. Intermediate-grade lymphomas, such as diffuse large cell tumors, have been successfully treated with combination chemotherapy, usually including doxorubicin. Such regimens often produce a complete response and long-term disease-free survival. Nevertheless, 30 to 50% of patients do not respond, and many have a relapse. Salvage chemotherapy is often unsuccessful. High-dose chemotherapy in conjunction with bone marrow transplantation is also an option for such patients.13

This case illustrates the usual aggressive nature and poor prognosis associated with T-cell lymphomas. Our patient died within 4 months after the onset of symptoms. He had generalized lymphoma that involved the lung, liver, paraaortic lymph nodes, and bone marrow. In contrast, primary pulmonary lymphomas are confined to the lung at the time of diagnosis; they are rare and are more commonly of B-cell subtype. Most often, these are low-grade tumors of bronchus-associated lymphoid tissue. Those with T-cell lineage, however, are associated with a less favorable course. Recent reports have described some association between presence of Epstein-Barr virus genome and development of T-cell lymphomas and several other types of lymphoproliferative disorders.10-12 In our patient, IgG antibodies to Epstein-Barr virus were present, but the significance of this finding is unclear. He had no risk factors for human immunodeficiency virus (HIV) infection, and serologic tests for HIV were negative. Although patients with AIDS have an increased frequency of occurrence of lymphomas, lung involvement by lymphoma is uncommon in these patients. Such lymphomas are usually of B-cell subtype and of high grade.

REFERENCES

Correct answers:
1. a, b, c, d, e