Residents' Clinic

62-Year-Old Man With Fever and Cough

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A 62-year-old man from the Middle East came to our emergency department because of a fever (39°C) and cough for 1 day, after having progressive weakness, malaise, and weight loss for 4 months. The patient had been well until 4 months previously, when he was found to be positive for human immunodeficiency virus (HIV) with confirmatory Western blot and a CD4 cell count of 76/µL. At that time, he had recurrent seizures caused by cerebral toxoplasmosis. The seizures stopped after implementation of therapy with pyrimethamine, sulfadiazine, phenytoin, zidovudine (AZT), and trimethoprim-sulfamethoxazole (TMP-SMX). After that hospitalization, he had become progressively weaker and had lost weight. AZT therapy was discontinued because of severe myalgias and anemia, the latter necessitating a blood transfusion. Because of development of a rash, the TMP-SMX was replaced by dapsone. His CD4 cell count declined to 25/µL 1 week before admission, at which time a chest roentgenogram revealed a new right middle and lower lobe infiltrate and hilar adenopathy, and clindamycin treatment was initiated. He had no known exposure to tuberculosis, and a tuberculin skin test had been negative 4 months previously. He had no headache, sputum production, or urinary symptoms. He reported no change in mental status and no visual disturbances.

On physical examination, the patient was in no apparent distress. His temperature was 38.6°C, heart rate was 90 beats/min, blood pressure was 120/70 mm Hg, and respiratory rate was 24/min. Lymph nodes in the head and neck area were not enlarged. Breath sounds were diminished in the posterior left lung base and the right midlung zone posteriorly and laterally. Egophony and bronchial sounds were detected over the right middle lobe. Cardiovascular and abdominal findings were normal, and no peripheral edema or erythema and no tenderness of the extremities were noted. Right inguinal lymphadenopathy was present.

1. Which one of the following diagnostic categories is least likely in this patient?
   a. Opportunistic infection
   b. Nonopportunistic infection
   c. Drug fever
   d. Connective tissue disease
   e. Malignant lesion

Patients with acquired immunodeficiency syndrome (AIDS) are susceptible to infections.1-3 The spectrum of infections varies with the CD4 cell count. Our patient with a CD4 cell count of 25/µL is susceptible to cytomegalovirus (CMV), herpes simplex, herpes zoster, toxoplasmosis, cryptoccocosis, reactivation of Mycobacterium tuberculosis, M. avium-intracellulare, and Pneumocystis carinii pneumonia (PCP) infections. Like nonimmunocompromised patients, he is also susceptible to common bacterial pathogens.1,3 A negative tuberculin test cannot exclude tuberculosis because most patients with AIDS have anergy late in their disease.1 Bacterial infections remain more common than opportunistic infections in patients with AIDS.1,2 Bacterial infections tend to cause more acute and severe illness, but considerable overlap of symptoms exists between opportunistic and nonopportunistic infections.1,3 Drug fever can be a complication of many medications including phenytoin, dapsone, and clindamycin. In an immunocompromised patient, this is not the most likely diagnosis but cannot be totally excluded. In view of the pulmonary infiltrate and the hilar masses, other diagnoses must be explored. Many connective tissue disorders can manifest with fever, malaise, and weight loss. Such disorders are not more common in patients with AIDS than in the general population, and they usually affect several body systems. In patients with the foregoing history, the incidence of connective tissue disease is much lower than the other listed diagnoses.4 Patients with AIDS have a substantially increased incidence of non-Hodgkin's lymphomas (NHLs), especially when they have low CD4 cell counts,5-6 and lymphoma can manifest with fever and weight loss.

Routine laboratory investigations on admission revealed the following: hemoglobin, 8.9 g/dL (normal, 13.5 to 17.5); leukocytes, 1.7 x 10³/L (normal, 3.5 to 10.5) with 22% segmented neutrophils (normal, 42 to 75%), 10% neutrophilic bands (normal, 0 to 3%), 20% lymphocytes (normal, 16 to 52%), 30% monocytes (normal, 1 to 11%), 16% eosinophils (normal, 0 to 7%), 1% basophils (normal, 0 to 4%),
and 1% myelocytes (normal, 0 to 0.5%); sodium, 130 mEq/L (normal, 135 to 145); aspartate aminotransferase, 48 U/L (normal, 12 to 31); chloride, 97 mEq/L (normal, 100 to 108); anion gap, 6 (normal, 7 to 15); and phenytoin, 4.2 mg/L (therapeutic, 10 to 20).

2. Which one of the following diagnostic tests is least appropriate at this point?
   a. Blood culture (routine and mycobacterial)
   b. Induced sputum for Gram stain and culture
   c. Chest roentgenography
   d. Flexible bronchoscopy with bronchoalveolar lavage (BAL) and bronchoscopic lung biopsy
   e. Arterial blood gases

Blood cultures and sputum Gram stain and culture are appropriate investigations in a febrile immunocompromised patient. Our patient did not appear very ill, but acute onset of fever necessitates investigations for infection. The lung is a common site for infection in immunocompromised patients. For bacteremia, early identification and aggressive treatment are important. Chest roentgenography is appropriate in a patient who has a recently discovered pulmonary infiltrate and new-onset fever. Identification of the pattern and progression of an infiltrate can have some implications for diagnosing a potential infection. Flexible bronchoscopy with BAL and bronchoscopic biopsy is highly sensitive and specific for most pulmonary infections; smears for PCP and acid-fast bacilli as well as CMV assay and identification of bacterial pathogens can be done with increased accuracy. In our patient, the yield might be decreased because of long-term PCP prophylaxis and antibiotic use. This test, however, is not indicated; simpler, less invasive diagnostic studies should be done first. Bronchoscopy could be performed if our patient were more ill or if the diagnosis could not be ascertained with other tests. Determining arterial blood gases can aid in the choice of subsequent interventions.

Our patient was placed in respiratory isolation. Cultures of blood (routine and mycobacterial) and urine were negative. Urine Gram stain and microscopy showed 1 to 3 erythrocytes (normal, less than 1). Sputum revealed flora with many leukocytes and few epithelial cells. A sputum smear for acid-fast bacilli was negative. Gram-negative bacilli identified as Klebsiella pneumoniae were cultured from the sputum. A chest roentgenogram (Fig. 1) revealed a right middle and lower lobe alveolar infiltrate that had progressed during a period of 1 week; nodules in the right lower and middle lobes were unchanged from the prior week. Arterial blood gas analysis showed an oxygen tension of 62 mm Hg, saturation of 89%, carbon dioxide tension of 37 mm Hg, bicarbonate of 24 mEq/L, and pH of 7.44 with the patient breathing room air. Administration of oxygen by nasal cannula normalized these values. Cefotaxime and erythromycin were given initially to cover community-acquired pneumonia pathogens, but after Klebsiella was identified in the sputum, erythromycin therapy was stopped. Oral pain and candidiasis prompted initiation of oral fluconazole therapy. Because of progressive respiratory symptoms, flexible bronchoscopy, BAL, and bronchoscopic lung biopsy were performed 2 days later. Smears for acid-fast bacilli and PCP as well as assay for CMV were negative. Respiratory isolation was then discontinued. Cultures and Gram stain from BAL were also negative, and the right middle lobe biopsy specimen showed some dense lymphoid tissue, with chronic inflammatory changes. A high-resolution computed tomographic (CT) scan of the chest revealed mediastinal lymphadenopathy, bilateral pulmonary nodules, a right hilar mass, and pulmonary infiltrates in the right lower and middle lobes. Abdominal CT findings were normal.

3. Which one of the following factors is least likely to be responsible for the patient's clinical course?
   a. Mycobacterium tuberculosis
   b. Bacterial pneumonia
   c. Lymphoma
   d. Pneumocystis carinii pneumonia
   e. Mycobacterium avium-intracellulare

The diagnosis of tuberculosis is consistent with our patient's initial manifestations, including fever, weight loss, and lymphadenopathy seen on CT. Tuberculosis in an immunocompromised host commonly disseminates and produces pulmonary infiltrates. Negative cultures 4 months earlier, current negative smears, and no known exposure to tuberculosis make the possibility of active tuberculosis less likely, without totally eliminating it. BAL and blood culture results were negative. The Klebsiella isolate from the spu-
Although it does not always cause clinically significant pneumonia, however, cannot explain all the CT and roentgenographic findings. Mediastinal lymphadenopathy is seldom caused by bacterial pneumonia or PCP; it is usually caused by fungal or mycobacterial infections or cancer. The fever and weight loss as well as findings on CT, roentgenogram, and physical examination could be attributable to lymphoma. Although lymphomas usually do not manifest as pulmonary infiltrates, this can occur in immunocompromised hosts. P. carinii is a common infection in immunocompromised hosts, particularly those with AIDS. It causes pneumonia in association with fever, ill-defined pulmonary infiltrates, and impaired gas exchange. Its course is progressive and rapidly fatal if not treated promptly with TMP-SMX or pentamidine. Our patient, however, had been compliant with prophylaxis for PCP. In addition, his Middle East origin somewhat diminishes the possibility of PCP, even though he was a part-time US resident. All sputa, BAL smears, and lung biopsy specimens for PCP were negative. PCP in patients with AIDS is characterized by high parasite loads, which make the sputum and the BAL smears extremely sensitive for AIDS-related PCP. Therefore, it is highly unlikely that our patient had PCP. Finally, infection caused by M. avium-intracellulare is a diagnostic possibility. It can cause fever and weight loss, and it is the most common infection when the CD4 cell count is less than 50/μL, although it does not always cause clinically significant disease. Our patient's symptoms and roentgenologic findings are compatible with such an infection.

Our patient continued to experience recurrent temperature elevations as high as 39°C on the fifth, sixth, and seventh days of the hospitalization while he was still receiving antibiotic treatment. Blood cultures remained negative.

4. Which one of the following is the most appropriate diagnostic step at this point?

a. Mediastinoscopy and mediastinal lymph node biopsy
b. CT-guided biopsy of mediastinal lymph nodes
c. Open-lung biopsy
d. Repeated bronchoscopy and bronchoscopic lung biopsy
e. Inguinal lymph node biopsy

Mediastinoscopy plus mediastinal lymph node biopsy is the most suitable procedure in this case. This procedure is done with the patient under general anesthesia, necessitates only a small incision, and is highly sensitive for diagnostic purposes. CT-guided biopsy of mediastinal lymph nodes and a lymph node aspirate are less invasive than mediastinoscopy, but the yield is variable, ranging from high for infections to low for malignant lesions (because of an inadequate amount of tissue). If a definite diagnosis is not obtained by such a procedure, it would be necessary to proceed with mediastinoscopy. Open-lung biopsy is the most sensitive diagnostic procedure because an adequate specimen of the target lesion as well as the surrounding perihilar nodes can be obtained. It was unclear, however, whether the pulmonary infiltrate was a pneumonia or was similar to the mediastinal lesion. Moreover, open-lung biopsy is an invasive procedure, requires general anesthesia, and would be associated with a higher morbidity and mortality in this patient than mediastinoscopy. In our patient, therefore, it is not the first procedure of choice. Bronchoscopy and lung biopsy had already been done a few days previously; a repeated procedure would probably not disclose the diagnosis. The inguinal lymph nodes were easily accessible, but the evidence of a primary process in the lung and mediastinum suggested that mediastinoscopy would be more useful.

Mediastinoscopy was performed. Frozen section analysis of lymph nodes was suggestive, but not diagnostic, of lymphoma. While the patient was still under anesthesia, the surgeon obtained consent from the patient's son and proceeded with open-lung biopsy of the right middle lobe to determine a more definitive diagnosis. Histologic analysis revealed an immunoblastic NHL of the B-cell phenotype (high grade). The patient tolerated both procedures very well. A hematolology-oncology consultation was requested after the diagnosis had been discussed with the patient.

5. Which one of the following is the best treatment option for this patient?

a. Allogeneic bone marrow transplantation
b. Chemotherapy with multiple drugs
c. Radiation therapy
d. Chemotherapy with a single orally administered agent
e. Resumption of AZT treatment

Bone marrow transplantation is a good treatment option for patients with non-AIDS-related lymphoma. Although little information is available on bone marrow transplantation in patients with AIDS, the first reports have not been promising. Multiagent chemotherapy is the preferred strategy for aggressive NHL in patients without AIDS. In patients with AIDS-related lymphoma and very low CD4 cell counts, however, this treatment has been shown to increase the mortality in comparison with no treatment. The morbidity and side effects of chemotherapy are also substantial—especially in a patient who is immunocompromised. Irradiation is often used to control localized lymphomatous lesions that are compressing vital structures. Our patient had widespread disease but no lesions compressing vital structures. Chemotherapy with a single orally administered agent is often used as a first-line treatment of low-grade NHL for extended periods of control with minimal side effects. In aggressive intermediate- and high-grade lymphomas, it offers no benefit over no treatment. AZT
increases survival and induces partial or, rarely, complete responses in patients with AIDS—but only in those with CD4 cell counts of more than 200/μL. Among the options offered, a trial of AZT was still the best for our patient.

Our patient's prognosis was very poor, as evidenced by his previous AIDS-defining condition and opportunistic infection, advanced stage (IV) and high-grade lesion, presence of "B" symptoms (weight loss and fever), extranodal involvement, marginal Karnofsky status, advanced age, and high pretreatment lactate dehydrogenase (877 U/L; normal, 112 to 257). He was only mildly symptomatic, and any effort at treatment would have intensified symptoms. Therefore, only supportive care and AZT therapy were recommended by the consultant in hematology-oncology.

The patient remained asymptomatic except for occasional febrile episodes, which were controlled with antipyretics. During AZT therapy, anemia redeveloped (hemoglobin, 7.5 g/dL); thus, use of AZT was discontinued. Two units of packed erythrocytes increased his hemoglobin level to 10.5 g/dL. The patient also had a minimally improved appetite. Antibiotic therapy was discontinued except for dapsone, pyrimethamine, and leucovorin (only prophylactic treatment was given because no active infection was evident). He was also given narcotic analgesics and stool softeners in view of his recent operation. He was dismissed 11 days after admission and was scheduled for outpatient follow-up. He was relatively asymptomatic 2 months later, but he then decided to return to his home country and was lost to follow-up.

DISCUSSION
This case illustrates an interesting manifestation of NHL. The patient had a subacute pulmonary infiltrate on a chest roentgenogram and an acute febrile illness. His immune system was suppressed, as evidenced by the low CD4 cell count and prior opportunistic infection. He was susceptible to new nonopportunistic and opportunistic infections, even though he was receiving prophylaxis for toxoplasmosis and PCP. His pulmonary infiltrate was suggestive of an infectious process, as were his sputum Gram stain and culture. His temperature initially responded to antibiotics. All these findings are consistent with an acute infectious process that responded to therapy. Careful review of the history and physical examination suggested a high possibility of a malignant condition as well. The weight loss and fever are consistent with it, and this impression was reinforced as his symptoms evolved and as more laboratory results became available. This case emphasizes the importance of a careful history and physical examination. It also highlights a fact about patients with AIDS: they frequently have more than one diagnosis that is responsible for their symptoms.

Lymphoma is a common neoplasm in patients with AIDS. NHLs are more common than Hodgkin's lymphomas. Lymphomas are thought to originate because of poor surveillance of the immune system on potentially malignant cells. Some lymphomas are associated with Epstein-Barr virus infection and malignant translocations; they are usually of the B-cell type and of intermediate or high grade. They are generally found in nodal sites in patients without HIV but are commonly extranodal in those with AIDS. Pulmonary lymphomas, like the one in our patient, are uncommon even among patients with AIDS. They respond poorly to treatment; the aggressive chemotherapy needed to eradicate them is often more harmful to patients than the lymphoma itself. With the current advances in antimicrobial therapy for opportunistic and viral infections, NHL is becoming a major cause of death in patients with AIDS.

Finally, an important aspect of this case is the ethnic and geographic origin of the patient. HIV infection and AIDS are uncommon or underreported in the Middle East. Therefore, the characteristics of patients with AIDS from that area are unknown because of the small numbers.

REFERENCES

Correct answers: 1, 2, 3, 4, 5, 6