A 31-Year-Old Man With Fever, Dyspnea, and Pulmonary Infiltrates

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A 31-year-old man sought medical assistance because of a 4-day history of low-grade fever, worsening dyspnea, and lethargy. For more than 6 months, he had had a chronic cough that produced mucopurulent sputum, the color and consistency of which had remained unchanged. A diagnosis of human immunodeficiency virus (HIV)-1 infection had been established 8 years previously, and antiretroviral therapy, consisting of two nucleoside analogues, had been administered for 1 year. He had suffered numerous episodes of pneumonia of unknown cause but had no history of Pneumocystis carinii pneumonia (PCP). He had been vaccinated against pneumococcal disease. His history was positive for thrush more than 6 months before the current examination but no recent episodes. He had no history of sweats or weight loss. Three months before admission, the CD4+ lymphocyte count was 170 cells/μL. He had been noncompliant with inhaled pentamidine for PCP prophylaxis. He admitted to a several-year history of abuse of orally administered narcotics, for which he was in a methadone program. He denied any current or past intravenous drug abuse. He reported an allergy to trimethoprim-sulfamethoxazole (TMP-SMX).

Physical examination revealed an obese man who appeared lethargic. He had a temperature of 37.9°C, pulse rate of 96 beats/min, blood pressure of 120/80 mm Hg, and respirations of 24/min. The oropharynx was normal. No lymphadenopathy was palpable. Faint crackles were detected at both lung bases. Cardiac examination showed normal findings, as did examination of the abdomen and extremities.

A chest roentgenogram revealed diffuse bilateral reticular and nodular densities with a basilar predominance (Fig. 1). The room air arterial oxygen tension (Pao2) was 73.8 mm Hg. The serum lactate dehydrogenase (LDH) level was 212 U/L (normal, 91 to 196).

1. Which one of the following statements is not true about this patient?
   a. Symptoms of PCP may be present for days to weeks before diagnosis
   b. The CD4 cell count places this patient at risk for PCP
   c. Basilar abnormal radiographic densities are inconsistent with a diagnosis of PCP
   d. Arterial blood gases may be normal in PCP
   e. Increased serum lactate dehydrogenase is common in PCP

   The clinical picture is consistent with PCP, which typically manifests in patients with acquired immunodeficiency syndrome (AIDS) as a subacute onset of fever, cough, and dyspnea. This patient’s CD4 cell count of less than 200 cells/μL and noncompliance with PCP prophylaxis put him at risk for PCP. In this setting, lung findings may be normal. The chest roentgenographic findings are also typical, with diffuse bilateral infiltrates that are usually perihilar or bibasilar. If the PCP is mild, arterial blood gases may be normal; alternatively, they may show hypoxemia, hypocarbia, and an increase in the alveolar-arterial O2 gradient. An increased LDH level with otherwise normal liver enzymes is a sensitive but nonspecific marker for PCP. It was only mildly increased in this patient.

2. Which one of the following conditions is least likely in this patient?
   a. Bacterial respiratory tract infection
   b. Tuberculosis (TB)
   c. Atypical mycobacterial infection
   d. Fungal infection
   e. Kaposi’s sarcoma

   Even though this patient’s manifestations are consistent with PCP, bacterial infection remains high on the list of potential diagnoses. The most common causes of pulmonary complications in patients with AIDS are similar to those seen in the general population—acute bronchitis, acute sinusitis, and bacterial pneumonia.1 The most common etiologic agents in bacterial pneumonia in patients with AIDS are Streptococcus pneumoniae and Haemophilus influenzae.2 Both of these bacteria usually cause lobar or segmental consolidation or infiltrates, although findings may be atypical in at least 25% of patients.3
Fig. 1. Posteroanterior chest roentgenogram obtained at time of admission, revealing diffuse bilateral reticular and nodular densities with a basilar predominance.

Our patient's manifestations would be unusual for TB. The clinical manifestations of TB in patients with AIDS vary with the degree of immunocompromise. Early in the course of HIV disease, the findings may be those of reactivation TB, with fever, productive cough, night sweats, weight loss, malaise, and disease confined to the lungs, and apical infiltrates or cavities may be evident roentgenographically. At this point, sputum is usually positive for acid-fast bacilli (AFB). In more advanced HIV disease, extrapulmonary manifestations of TB are common, usually in conjunction with pulmonary disease. The chest roentgenogram may show any pathologic pattern or normal findings. Sputum may be negative for AFB.

Mycobacterial infections other than TB should also be considered. Although our patient did have fever and dyspnea, his clinical picture is inconsistent with Mycobacterium avium complex, which most often manifests with fever, anorexia, weight loss, and night sweats in patients with AIDS and is rarely confined to the lungs in this population. M. kansasii may manifest with pulmonary disease alone in 60 to 74% of patients and causes fever, night sweats, weight loss, fatigue, productive cough, dyspnea, chest pain, and occasional hemoptysis.

Fungal infections most likely to cause the findings noted in our patient are Coccidioides immitis, Blastomyces dermatitidis, Histoplasma capsulatum, and Cryptococcus neoformans. Both coccidioidomycosis and blastomycosis are unlikely for geographic reasons, with the former endemic in the southwestern United States, northwestern Mexico, Argentina, and Central America and the latter found in the Mississippi, Ohio, and Missouri river valleys. Our patient denied any travel to these regions from his home in northern Florida. In patients with AIDS and histoplasmosis, the infection is disseminated in 95% of cases and causes cough and dyspnea in 50%. The chest roentgenogram may show normal findings or any pattern of abnormality. Aspergillosis is also possible, the lung being the most common site of infection in patients with AIDS and roentgenographic findings again being nonspecific. Cryptococcus causes meningitis in 72 to 90% of patients infected with AIDS, usually manifesting subacutely with fever and headache. Pulmonary disease, present in 30 to 45% of cases, consists of nonproductive cough, dyspnea, and roentgenographic demonstration of diffuse interstitial or alveolar infiltrates, nodular densities, cavities, lymphadenopathy, or pleural effusions.

Although Kaposi's sarcoma may involve the lungs, pulmonary involvement without cutaneous involvement would be unusual. Our patient had no skin lesions on examination; therefore, Kaposi's sarcoma would be the least likely diagnostic choice.

3. Which one of the following is the most appropriate next step in the management of this patient?
   a. Await results of sputum analysis
   b. Initiate amphotericin treatment
   c. Begin trimethoprim-sulfamethoxazole therapy
   d. Give 2 g of methylprednisolone intravenously and begin therapy with inhaled pentamidine
   e. Start therapy with a third-generation cephalosporin and a macrolide as well as empiric treatment for PCP

The diagnosis at this point remains uncertain, but bacterial pneumonia and PCP are most likely. Empiric treatment of PCP is suggested in clinical scenarios that include a recent history of dyspnea on exertion or nonproductive cough, diffuse interstitial pulmonary densities, arterial hypoxemia, and no evidence of bacterial pneumonia. Because our patient met these criteria, withholding treatment while awaiting the results of sputum analysis would be inappropriate. Therapy with a toxic medication such as amphotericin is also inappropriate; the possibility of fungal infection is low at this point in the patient's assessment.

The first line of therapy for PCP is TMP-SMX, but our patient reported an allergy to this drug. In patients with severe PCP, intravenously administered pentamidine is recommended despite potential toxicity. Inhaled pentamidine, although sometimes useful for prophylaxis, is ineffective for PCP. Corticosteroid therapy should be initiated in cases of moderate to severe PCP, when the Pao₂ is less than 71 mm Hg or the alveolar-arterial O₂ gradient is more than 35 mm Hg. In our patient, the Pao₂ was 73 mm Hg; thus, corticosteroids were deemed unnecessary. Standard coverage for community-acquired pneumonia, with use of a third-generation cephalosporin and a macrolide, should also be provided until a diagnosis of PCP is firmly established.
Empiric treatment with intravenously administered pentamidine, erythromycin, and ceftriaxone was begun. The patient's clinical condition showed no appreciable improvement but remained stable.

4. Which one of the following diagnostic procedures would be most appropriate at this time?
   a. Sputum induction
   b. Bronchoalveolar lavage (BAL)
   c. Serologic studies for PCP
   d. Blood cultures
   e. Computed tomography (CT) of the thorax

   The most appropriate next step in this situation is to confirm or eliminate the diagnosis of PCP. The success of sputum induction, a technique in which 3 to 5% saline is administered by means of a nebulizer, is dependent on both the experience of the technician and the cooperation of the patient, which may be difficult when dyspnea or bronchospasm is present. The sensitivity of this test may also be decreased by PCP prophylaxis with aerosolized pentamidine. Sputum for AFB and Gram stain should also be obtained.

   BAL has a sensitivity of 79 to 98% for the diagnosis of PCP and is the procedure of choice when no sputum is available or when no pathogen is identified by sputum analysis. The sensitivity may be decreased in patients receiving prophylaxis for PCP with aerosolized pentamidine. Detection of serum antibodies to PCP generally indicates exposure and is not useful in determining the presence of disease. Blood cultures for routine and fungal organisms should have been obtained before initiation of antibiotic therapy. A CT scan should be considered if the diagnosis is not apparent after bronchoscopy and BAL.

   Sputum induction was unsuccessful in our patient. On the second hospital day, flexible bronchoscopy with BAL revealed mucopurulent secretions throughout the bronchial tree. Microbiologic studies, including stains for PCP, were negative. On the fourth hospital day, CT of the thorax revealed abnormal bilateral lung opacities, predominantly in the lower lobes posteriorly, with a reticular and nodular appearance (Fig. 2). Lymph nodes measuring less than 2 cm were noted in the anterior mediastinum.

5. Which one of the following is the most appropriate next step in managing this patient?
   a. Mediastinoscopy
   b. Needle biopsy
   c. Empiric treatment with amphotericin
   d. Empiric treatment with corticosteroids
   e. Open-lung biopsy

   The lymph nodes noted on CT scan were small; the yield on biopsy is generally low when nodes are smaller than 2 cm in diameter. Needle biopsy would be difficult and perhaps nonproductive because no large, discrete lesions were present. Amphotericin can be toxic and should not be used without clear evidence of fungal infection. Empiric treatment with corticosteroids could be harmful in an immunocompromised patient in whom infection has not been ruled out completely. Open-lung biopsy is the most appropriate next step in order to obtain adequate tissue for pathologic and further microbiologic studies.

   On the seventh hospital day, an open-lung biopsy was performed. Histologic review revealed granulomatous pneumonitis with foreign body giant cell reaction and crystalline foreign body material consistent with talc granulomatosis (Fig. 3).

   After receiving full courses of therapy for both possible PCP and bacterial pneumonia, the patient was dismissed from the hospital. He continued to have moderate dyspnea.
DISCUSSION
Talc (magnesium silicate) is used as a filler and lubricating agent in the tablet form of many medications. Intravenous injection of drugs intended for oral use may lead to talc granulomatosis. Drugs abused in this manner include methadone, pentazocine, hydromorphone, propoxyphene, methylphenidate, and amphetamines. Talc particles embolize to the lungs and become trapped in pulmonary arterioles and capillaries, resulting in endothelial injury, inflammation, and thrombosis. In time, the talc particles may migrate through the vessel walls into the pulmonary interstitium. Thus, this disorder involves diffuse intravascular and perivascular noncaseating granulomas, with resultant interstitial fibrosis and pulmonary hypertension.

Clinical features of talc granulomatosis are usually confined to the lungs and appear only after heavy or prolonged use, with the cumulative injection of 10,000 to 100,000 tablets. The most common manifestation is progressively worsening dyspnea on exertion, which may be associated with a slightly productive cough. Because most of these patients are smokers, the cough may not be caused by the granulomatous disease. From repeated intravenous injections, most patients with this condition will have scarring of the forearms vessels. On examination of the optic fundi, glistening white dots, which represent talc particles in the macular region, may be seen in 60% of patients.

Chest roentgenographic findings may vary and may be normal in 50 to 65% of patients. Abnormal findings may include diffuse reticular and nodular infiltrates, with nodules less than 1 mm in diameter and an upper or lower lobe predominance. Later, the nodules may coalesce and produce large areas of consolidation, with findings similar to those of progressive massive fibrosis. Patients may also have emphysematous changes and bullae formation.

Findings on high-resolution CT have been described in three patients: diffuse ground-glass pattern without discrete nodules in one; confluent perihilar masses consistent with end-stage sarcoidosis in another; and conglomerate perihilar masses with distorted lung architecture, septal thickening, diffuse fine micronodules, and moderately severe emphysematous changes in the peripheral lung fields of the third. In the last two cases, the perihilar masses contained areas of high attenuation, consistent with talc deposition. The third case was not confirmed by lung biopsy, but talc emboli were observed on ophthalmoscopy.

Pulmonary function testing usually reveals a decreased diffusing capacity for carbon monoxide. A decrease in perfusion may be seen on radionuclide scanning. Obstruction is the most common ventilatory abnormality, but restrictive and mixed defects have also been reported.

Definitive diagnosis is by biopsy (usually transbronchial or open-lung biopsy) although fine-needle aspiration has reportedly been useful. Pathologic specimens show multiple foreign body granulomas that contain birefringent crystals. BAL has been diagnostic in some series, with intracellular or free birefringent particles seen in the fluid collected from 66% of patients. Other fillers in tablets, such as starch and cellulose, may cause similar reactions, with birefringent particles apparent on polarized microscopy. The reaction caused by starch is usually transient. Talc, cellulose, and starch can be distinguished from one another by histochemical staining techniques.

In an immunocompromised host, such as the patient described in this report, early findings of pulmonary talc granulomatosis can mimic many opportunistic infections, including PCP, cytomegalovirus, TB, atypical mycobacterial infections, and disseminated fungal infections. In later stages, this disorder may be confused with TB, chronic cavitary histoplasmosis, chronic necrotizing aspergillosis, or melioidosis. Therefore, a high index of suspicion is important in making the diagnosis.

The changes of pulmonary talcosis are irreversible. Untreated disease may progress, despite cessation of intravenous drug abuse, and pulmonary hypertension, cor pulmonale, and death may ensue. Oral treatment with corticosteroids has been reported to decrease symptoms and complications in a few cases.

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REFERENCES

Correct answers: 1, c, 2, e, 3, e, 4, a, 5, e