33-Year-Old Man With Cough, Fever, and Weight Loss

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A 33-year-old man presented to our medical center with 3 months of nonproductive cough, anorexia, fatigue, night sweats, and a 6.8 kg weight loss. The patient's symptoms began on a deer hunting trip in the fall in northern Minnesota, when he reclined on a patch of earth that he had cleared of copious organic matter. Immediately on returning from his trip, he was fatigued and slept 18 hours per day. One week later he developed night sweats, anorexia, and nonproductive cough, prompting a visit to his primary care physician. The patient was treated with 7 days of levofloxacin but his condition did not improve. He was then treated with a 5-day course of azithromycin, which provided no relief. The patient's symptoms continued to persist 5 weeks after the hunting trip, at which time several of his hunting buddies were diagnosed with ehrlichiosis. A 21-day course of doxycycline for presumed ehrlichiosis did not relieve his symptoms. Eight weeks after his hunting trip, the patient developed a small subcutaneous lesion on his right anterior chest area and fluctuant swelling over his left first metatarsophalangeal joint. This fluid collection was drained but not cultured or analyzed for crystals. Despite this, he was treated empirically for gout with prednisone, colchicine, and oral cephalexin. Soon after, he developed left great toe pain and swelling and a new lip lesion. Magnetic resonance imaging performed by his primary care physician revealed an abscess involving the first metatarsophalangeal joint of the left foot without evidence of osteomyelitis. Consequently, the foot was surgically debrided and a central catheter line was placed. Colchicine, prednisone, and cephalexin were discontinued and intravenous cefazolin was initiated to treat the residual abscess. A week later the patient had not improved and his surgical wound was not healing, so he was admitted to our hospital for further care.

On physical examination the patient was afebrile, normotensive, and normocardic. Skin examination showed a lesion on the upper lip and a noninflammatory surgical wound with exposed tendons on the dorsum of the left foot. Cardiac examination revealed no murmurs or other abnormal sounds, and the lungs were clear. The abdomen was soft without organomegaly or masses. No adenopathy was observed and the neurological examination was nonlocalizing. Notable laboratory findings (reference ranges shown parenthetically) were as follows: hemoglobin, 15.1 g/dL (13.5-17.5 g/dL); leukocytes, 16.2×10^9/L (3.5-10.5×10^9/L); neutrophils, 13.1×10^9/L (1.7-7.0×10^9/L); platelets, 306×10^9/L (150-450×10^9/L); sedimentation rate, 61 mm/h (0-22 mm/h); C-reactive protein, 12.8 mg/dL (<0.8 mg/dL); alanine aminotransferase, 45 U/L (10-45 U/L); aspartate aminotransferase, 25 U/L (12-31 U/L); alkaline phosphatase, 83 U/L (45-115 U/L); sodium, 137 mEq/L (135-145 mEq/L); potassium, 4.5 mEq/L (3.6-4.8 mEq/L); creatinine, 1.0 mg/dL (0.9-1.4 mg/dL); and uric acid, 5.8 mg/dL (4.3-8.0 mg/dL). Findings on peripheral blood smear and urinalysis were unremarkable. A chest radiograph showed diffuse bilateral miliary nodular infiltrates.

1. Which <u>one</u> of the following would be the <u>most likely</u> diagnosis at this point?

a. *Testicular cancer*
b. *Sarcoidosis*
c. *Wegener granulomatosis*
d. *Vitamin C deficiency*
e. *Disseminated infection*

The patient had symptoms, including fatigue, night sweats, and weight loss, that were possibly consistent with malignancy. Testicular cancer has the highest incidence in males aged 15 to 35 years, and metastatic disease is not uncommon. However, this patient had no testicular mass, making this diagnosis unlikely. The patient's nonproductive cough, fever, and weight loss could also be consistent with sarcoidosis. However, the reticulonodular infiltrate pattern revealed on chest radiograph, the absence of hilar lymphadenopathy, and the skin lesions that were inconsistent with erythema nodosum (the most common skin finding in sarcoidosis)[1] virtually exclude this diagnosis. The patient's presentation leads one to consider Wegener granulomatosis, yet his lack of upper respiratory symptoms and vasculitic rash and the unremarkable findings on urinalysis make this diagnosis unlikely. Moreover, the characteristic chest radiograph pattern in Wegener granulomatosis would be an alveolar pattern, not the reticulonodular pattern seen on our patient's chest radiograph.[2] In the United States, vitamin C deficiency is generally limited to severely malnourished patients, such as chronic alcoholics and the impoverished. Although constitutional symptoms

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See end of article for correct answers to questions.

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can be seen in patients with vitamin C deficiency, our patient lacked other classic findings such as bleeding gums, ecchymoses, petechiae, hyperkeratosis, joint swelling, and edema. A disseminated infection was deemed the most likely diagnosis because of our patient's substantial exposure to decaying organic matter, the temporal relationship of symptoms to exposure, the pulmonary and peripheral involvement, and the constitutional symptoms including fevers, malaise, and night sweats.

We performed additional tests, including blood cultures, induced sputum smears/culture, and urine culture. Serologic findings for the patient were as follows: antinuclear antibodies, 0.2 U (<1.0 U, negative); rheumatoid factor, less than 15 IU/mL (<15 IU/mL); anti–double-stranded DNA, 1.0 IU/mL (<25.0 IU/mL, negative); and α fetoprotein, within normal limits. Because a source of infection was not evident and the patient was not critically ill, antimicrobial treatment was withheld.

2. Which one of the following would be the most appropriate next diagnostic test?

a. *Bronchoscopy*
b. *High-resolution computed tomography of the chest*
c. *Computed tomography of the head*
d. *Bone marrow biopsy*
e. *Urinary Legionella antigen enzyme immunoassay*

Bronchoscopy with bronchoalveolar lavage for cytology and culture would be indicated if, unlike in our patient, the diagnosis could not be obtained by less invasive means or if the patient's condition failed to improve despite appropriate antibiotic therapy. High-resolution computed tomography of the chest would be the preferred diagnostic test because it would help to further characterize the abnormal chest radiograph findings of diffuse bilateral reticulonodular infiltrates, thereby facilitating a differential diagnosis.[3] Computed tomography of the head would not be indicated for this patient because he had no symptoms or physical findings to suggest an intracranial process. Our patient's fever and weight loss could be due to a hematologic disorder; however, a bone marrow biopsy would not be indicated in the absence of lymphadenopathy and otherwise unexplainable abnormalities of complete blood cell count and peripheral blood smear. Infection with *Legionella pneumophila* generally involves an incubation period of 2 to 10 days, and radiographic findings of a lobar pneumonia are commonly seen within 3 days. Furthermore, a previous study revealed that while the *Legionella* urine antigen is helpful in diagnosing Legionnaires' disease in severe pneumonia (sensitivity, 85.7%), it may not be as helpful in diagnosing mild or moderate pneumonia (sensitivity, 37.9% and 40.5%, respectively).[4] Our patient's insidious course and lack of central nervous system (CNS) and abdominal symptoms made Legionnaires' disease unlikely.

Computed tomography of the chest revealed numerous micronodules scattered throughout both lungs and enlarged bilateral hilar and subcarinal lymph nodes.

3. Which one of the following infections is most likely in this patient?

a. Blastomyces
b. Cryptococcus
c. Coccidioides
d. Francisella tularensis
e. Mycobacterium tuberculosis

Patients with disseminated blastomycosis, which is endemic to a broad area of the United States including the Mississippi and Ohio river valleys, often present with weight loss, fatigue, fevers, night sweats, and malaise. Chest radiographs may reveal, in order of decreasing frequency, alveolar infiltrates, a mass, or reticulonodular infiltrates.[5] Cutaneous lesions typically occur after the pulmonary infection and are generally verrucous or ulcerative. Microscopy and culture of biopsy specimens usually reveal *Blastomyces.* Blastomycosis is associated with exposure to soils and decaying organic matter. For all these reasons, our patient was thought to have blastomycosis. Both symptomatic pulmonary and disseminated infection with *Cryptococcus* are very rare in immunocompetent persons and so would be less likely in our patient. Common findings on chest radiograph include noncalcified nodules.[6,7] *Coccidioides* is endemic to lower desert areas of the Western Hemisphere, ie, the southwestern United States, Mexico, and arid regions of Central and South America. Our patient denied travel outside of Minnesota.

Tularemia can masquerade as many other diseases. Patients frequently develop fevers, chills, headaches, fatigue, and generalized aches. Ulcers and eschars can form at the site of an insect bite or inoculation, resulting in dissemination to regional lymph nodes, spleen, liver, kidneys, lungs, the CNS, small and large bowels, and skeletal muscles.[8] *F tularensis* has been isolated from rabbits, hares, beavers, muskrats, water voles, rats, squirrels, lemmings, and mice. The United States averages 124 cases of tularemia annually, with 56% of cases occurring in the states of Arkansas, Missouri, South Dakota, and Oklahoma.[9] Our patient had no exposures or travel to suggest tularemia.

Tuberculosis commonly presents with fatigue, cough, fevers, night sweats, and weight loss, symptoms similar to those observed in our patient. Primary tuberculosis is usually associated with lymphadenopathy and lower-lobe infiltrates on chest radiograph, whereas secondary tuberculosis is often associated with upper-lobe infiltrates and cavitation. Bilateral diffuse miliary nodules, as seen in our patient, would be

unlikely.[10] Furthermore, tuberculosis in US patients usually occurs in immigrants from developing countries, institutionalized patients, and the immunocompromised.[11] Our patient had none of these diagnostic features.

Serologic test results were negative for *Histoplasma*, *Cryptococcus*, *Coccidioides*, and *Francisella* serum antibodies but positive for *Blastomyces* serum antibodies (titer, 1:16). The results of a purified protein derivative tuberculin skin test (performed at another institution) and of a QuantiFERON-TB test (Cellestis Limited, Carnegie, Australia) were both negative. Induced sputum samples were obtained on days 3 and 4 of hospitalization, and both the DNA probe and cultures were positive for *Blastomyces dermatitidis*. Furthermore, biopsy of the upper lip lesion showed budding fungal elements consistent with, and a DNA probe positive for, *B dermatitidis.*

4. Which one of the following is the most appropriate medical treatment for this patient's disease?

a. *Amphotericin B for 1 month*
b. *Amphotericin B until clinical improvement, then itraconazole for 6 months*
c. *Ketoconazole for 3 months*
d. *Fluconazole for 6 months*
e. *Itraconazole for 6 months*

Patients with life-threatening disease or CNS involvement are treated with amphotericin B until the condition improves. Because our patient had no CNS involvement or severe pulmonary infection, his disease would be classified as mild to moderate and would not necessitate treatment with amphotericin B. All 3 of the azoles listed in the questions are effective for treating blastomycosis; however, fluconazole and itraconazole are less toxic than ketoconazole. Fluconazole achieves more CNS penetration and may be considered for patients with CNS involvement; however, it is less effective than itraconazole and ketoconazole. Because our patient had no CNS involvement, itraconazole would be the drug of choice. A common serious reaction to itraconazole is hepatotoxicity. Frequently seen adverse effects include gastrointestinal symptoms (nausea, diarrhea, and abdominal pain), rash, headache, and fever. In addition to elevated liver biochemistries, laboratory abnormalities include hypokalemia and elevated creatinine and triglyceride levels. The patient was treated with 400 mg/d of oral itraconazole with an anticipated course of at least 6 months.[12]

5. Which one of the following statements about this patient's disease is true?

a. *A negative serum antibody for* Blastomyces *excludes the diagnosis*
b. *Identification of* Blastomyces *in sputum is diagnostic for pulmonary blastomycosis*
c. *Diagnostic yield from bronchoscopy and bronchoalveolar lavage is substantially higher than from sputum for pulmonary blastomycosis*
d. *Blastomycin skin test has an adequate sensitivity and specificity for blastomycosis to be used as a screening test*
e. *Culture results can be considered negative after a 2-week incubation*

Early studies of immunodiffusion and complement fixation of serum for *B dermatitidis* demonstrated 80% sensitivity, yet subsequent studies have shown that the sensitivity is substantially less.[13] Unlike other fungi such as *Candida*, *Blastomyces* is not believed to colonize the respiratory tract, and identification of fungal elements in sputum culture confirms the diagnosis. In a review of 119 confirmed cases of pulmonary blastomycosis at Mayo Clinic, investigators demonstrated a diagnostic yield of 75% for cultures of a single sputum sample or tracheal secretion, which increased to 86% when 2 or more samples were obtained.[14] Culture of bronchial washings yielded a diagnosis in 100% of cases, culture of bronchoalveolar lavage in 67%.[14] No substantial difference was observed in this study between the yield of tracheal secretions and bronchial washings. The blastomycin antigen is no longer used for skin testing because it has poor sensitivity and specificity.[12] Cultures for *B dermatitidis* must be incubated for at least 5 weeks.[15] In our patient, sputum smears, culture, skin biopsy specimens, and serum *Blastomyces* antibody titers all supported the diagnosis of disseminated blastomycosis.

After several days of itraconazole therapy in the hospital, the patient's fever and night sweats resolved, his foot and lip lesions began to heal, and his fatigue substantially improved. He was discharged from the hospital to complete 6 months of itraconazole therapy and was noted to be recovering on follow-up in the outpatient clinic.

DISCUSSION

Blastomyces dermatitidis is generally confined to North America and is endemic to the Mississippi, Ohio, and St Lawrence river watersheds. The fungus is found in moist soil that is rich in organic matter. In one notorious outbreak of pulmonary blastomycosis at an environmental camp in northern Wisconsin, the disease was linked to exposure to moist soil and decomposed wood surrounding a beaver dam.[16] In another outbreak, disease was linked to exposure to riverbank soils that, on further investigation, were confirmed to harbor *B dermatitidis*.[17] Other risk factors are residence in or travel to an endemic area, outdoor employment or recreation,[18] and exposure to soil during home construction.[19] Between 1986 and 1995, 670 cases of blastomycosis were reported in Wisconsin, 95% of which were confirmed.[18] The mortality rate increased with age, from

3.4% for those aged 45 to 64 years to 12.5% for those older than 65 years, with an overall mortality rate of 4.3%. The incidence and mortality rates of blastomycosis were found to be similar in a review of 72 cases in northeast Tennessee.[19] The prevalence of asymptomatic or self-limited disease is probably rare.

Blastomycosis often masquerades as other diseases such as pulmonary malignancy and cutaneous squamous cell carcinoma. For example, our patient was treated for gout and several presumed infections including ehrlichiosis before the proper diagnosis was reached. Common presenting symptoms include cough, weight loss, fever, night sweats, pleuritic chest pain, and skin lesions. The organ systems involved in patients with blastomycosis vary. Indeed, in one series 76% of patients showed solely pulmonary disease, 18% solely extrapulmonary disease, and 6% both pulmonary and extrapulmonary disease.[18] The most frequent sites of extrapulmonary involvement are, in descending order, skin, bone, the genitourinary tract, and the CNS.[18] Pulmonary blastomycosis may be acute or chronic, and numerous findings are possible on chest radiograph. For instance, in one series of patients who presented with acute pulmonary blastomycosis, radiographs revealed alveolar infiltrates in 68%, masslike findings in 15%, and interstitial infiltrates in 13%. Notably, patients with chronic pulmonary blastomycosis were more likely to have masslike findings (34%). Among patients who presented with chronic or acute pulmonary blastomycosis, findings were unilateral in 77% of those with alveolar infiltrates and in 90% of those with masslike lesions.[20] Also, upper-lobe infiltrates were significantly more likely than middle- or lower-lobe infiltrates.[20] Cutaneous blastomycosis includes ulcerative and verrucous lesions, the latter of which (as in our patient) often overlie a subcutaneous abscess.[12]

The diagnosis of blastomycosis is confirmed by isolating *B dermatitidis* from the respiratory tract or skin. Characteristic broad-based, budding yeast forms in smears or biopsy specimens are generally considered adequate for diagnosis. Culture of *Blastomyces* from any site is the criterion standard. Although *Blastomyces* grows on Sabouraud dextrose agar (the standard medium for pathogenic fungi), its culture can take up to 5 weeks. Obtaining multiple sputum samples is the preferred diagnostic approach, but the diagnostic yield of skin biopsy specimens is also high. The diagnosis of blastomycosis using bronchoscopy, either with or without bronchoalveolar lavage, has not proven superior to multiple sputum samples. However, if clinical suspicion is high and sputum samples are negative, bronchoscopy should be pursued.[14]

Introduced in the 1980s, ketoconazole offers an effective oral treatment that is less toxic than amphotericin B. Some of the more recent azoles and triazoles are as effective as ketoconazole and may be less toxic. Newer azoles such as voriconazole have excellent activity against *Blastomyces*. Although fluconazole is less effective than ketoconazole and itraconazole, it has better CNS penetration. The 2000 Infectious Diseases Society of America Practice Guidelines for the Management of Patients with Blastomycosis[21] recommend at least a 6-month course of itraconazole for mild to moderate pulmonary and disseminated infections. Amphotericin B is recommended for patients with life-threatening disease or CNS involvement, followed by itraconazole when the patient stabilizes. Fluconazole may be considered in cases of isolated CNS involvement.[21]

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Correct answers: 1. *e*, 2. *b*, 3. *a*, 4. *e*, 5. *b*