

Acute Respiratory Distress Syndrome from Blastomycosis: A Case Report

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INTRODUCTION

Blastomyces dermatitidis. The most heavily endemic areas in the world are in the United States.¹ These include the Mississippi and Ohio River Valleys and around the Great Lakes and extends to northern Wisconsin and northern Minnesota. Fungal growth occurs in nitrogen-rich soil close to streams, rivers and lakes, and aerosolization is facilitated by rain, excavation or other disturbance of a site with contaminated soil. Except for rare cases of direct inoculation into soft tissue, the lung is the portal of entry and the site of the primary disease.¹ About one half of those infected are asymptomatic, and in others, the symptoms vary in severity. Rarely, blastomycosis causes a severe and fulminant pneumonia that presents as acute respiratory distress syndrome (ARDS) with dyspnea, tachypnea, diffuse pulmonary infiltrates, severe hypoxemia and respiratory failure. This case report describes the features of such a presentation and highlights the diagnostic aspects.

CASE REPORT

A 70-year-old man was transferred to the Milwaukee Veterans Affairs Medical Center (VAMC) from the Iron Mountain, Michigan VAMC for management of a pneumonia that worsened in spite of antibiotic treatment. He had a fever, chills and non-productive cough for 1 day, and weakness and mild diarrhea for 1 week prior to admission to the Iron Mountain VAMC. Initial chest radiograph was normal, but right middle and lower lobe infiltrates appeared within a day of admission. He had leukocytosis

(18,000/mm³) and urine culture showed 30,000 colonies of enterococcus. The patient was treated empirically for community acquired pneumonia and urinary tract infection with intravenous ampicillin/sulbactam, ceftazidime and gentamicin. However, he developed progressive infiltrates on chest x-ray and was transferred to the Milwaukee VAMC on the fourth hospital day.

His past medical history was relevant for myelodysplastic syndrome (refractory anemia with excessive blasts) diagnosed 8 months ago, diabetes mellitus type 2 and hypertension. He lived in Iron Mountain, MI and worked in a shoe repair shop. He had quit smoking 4 to 5 years ago after a total of 100 pack-years and did not use alcohol.

On admission to the Milwaukee VAMC, he had a temperature of 103.6°F; heart rate 88/min; blood pressure 130/80 mmHg and respiratory rate 24/min. He was on 6 liters per minute of oxygen via nasal cannula and had a pulse oximetry reading of 92%. He had mild jugular venous distension and splenomegaly. He had decreased breath sounds in the left lower lung zone posteriorly and bibasilar rales. There were no skin lesions. Laboratory evaluation revealed a white blood cell count of 30,000/mm³ with 82% neutrophils and 8% bands; hematocrit 27% and platelets 78,000. The basic chemistry results were unremarkable, as was the urinalysis. The lactate dehydrogenase (LDH) was elevated at 900 international units. Chest x-ray showed bilateral diffuse interstitial and alveolar infiltrates, most prominent in the right mid-lung zone (Figure 1). Sputum could not be provided for examination. Other tests obtained include blood cultures, stool culture for ova and parasites, viral study of nasopharyngeal secretions and urine legionella antigen.

The clinical impression upon admission to the Milwaukee VAMC was of progressive community acquired pneumonia. To provide coverage for atypical organisms, azithromycin was added to the regimen. However, the patient became progressively tachyp-

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neic and his FIO₂ requirements to maintain an SaO₂ > 90% increased during his first hospital day in the Milwaukee VAMC. An arterial blood gas analysis early the second hospital day on an FIO₂ of 60% was pH 7.45, PO₂ 57, PCO₂ 33, SaO₂ 92%. Since the patient's pneumonia appeared to be progressing despite broad antibiotic coverage, a fiberoptic bronchoscopy with bronchoalveolar lavage was performed in an attempt to identify an infectious agent on the second hospital day. Microscopic study of lavage fluid with potassium hydroxide (KOH) showed many broad-based budding yeasts characteristic of *Blastomyces dermatitidis*. Blood cultures were sterile. The patient was started on intravenous amphotericin B (0.5 mg/kg/day).

Over the next day, the patient's respiratory failure worsened and intubation and mechanical ventilation was initiated. Septic shock developed and his condition deteriorated over the next 2 days. Mechanical ventilation was withdrawn after discussion with family, and the patient died 7 days after admission. He had received a total dose of 40 mg amphotericin B and 700 mg of liposomal amphotericin. Postmortem examination of the lungs showed numerous budding and non-budding yeasts in a background of extensive inflammation, granuloma formation and necrosis (Figure 2). Yeasts of *Blastomyces dermatitidis* were also seen in the liver but not in the spleen. An examination of the bone marrow did not reveal transformation of the myelodysplastic syndrome to leukemia.

DISCUSSION

Pulmonary disease is the most common manifestation of blastomycosis. Isolated lung disease occurs in about 77% of infected people.² In the remaining group, dissemination to skin, bones, genitourinary system and other organs is seen. Pulmonary infection is asymptomatic in 50% of the patients.³ In the remaining patients, the disease may present in any of the following forms: (a) a brief flulike illness with rapid resolution, (b) acute illness resembling bacterial pneumonia, (c) subacute or chronic illness resembling tuberculosis or lung cancer (most cases of sporadic blastomycosis fall into this category), or (d) fulminant infectious ARDS.

Meyer and colleagues described their experience with 10 patients who lived in Wisconsin or the upper peninsula of Michigan and had blastomycosis that caused ARDS with fever, cough, and dyspnea associated with profound impairment of oxygenation (mean alveolar-arterial gradient of 616 mm Hg).⁴ Review of 25 such cases in the literature showed that 28% of the patients were immunocompromised. Most patients



Figure 1. Anterior-posterior chest radiograph on admission to the Milwaukee VAMC showing bilateral interstitial and intraveloar pulmonary infiltrates.

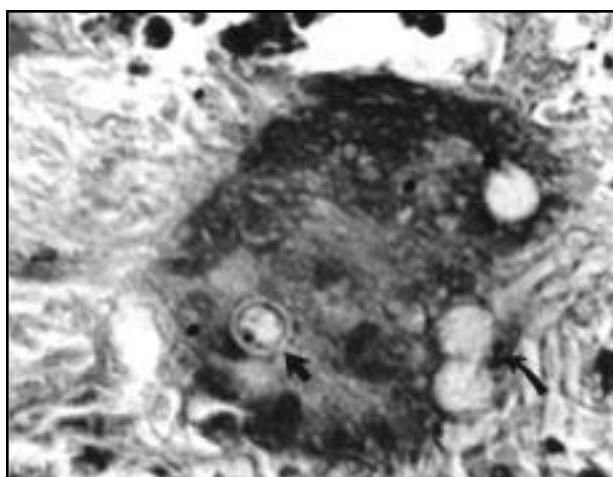


Figure 2. High magnification view (H&E stain, 400x) of lung taken at autopsy demonstrating a multinucleated giant cell. The cell contains numerous *Blastomyces dermatitidis* organisms, including one with appearing to have a double wall (short arrow) and another as a broad-based budding yeast form (curved arrow).

were not immunocompromised and did not have any serious underlying disease. Although it is not known why some persons develop this fulminant form of the disease, it is likely that a large inoculum and a large amount of antigens that activate suppressor cells are responsible factors.⁵

Microscopic examination of a wet mount preparation with KOH of the sputum is the single most important diagnostic test. The yeast form of the fungus was detected in 95% of the cases ARDS caused by blastomycosis when the sputum was available and examined.⁴ As the morphologic appearance of the yeasts, 8 to 20 μm in size, with single broad based buds, double refractile walls and multiple nuclei are

very characteristic of *B. dermatitidis*, treatment can be started without delay. Confirmation by culture takes many days to weeks. If sputum is unavailable, it is important to rapidly proceed with fiberoptic bronchoscopy and bronchoalveolar lavage. Besides wet mounts with KOH, periodic acid Schiff (PAS) and silver stains are useful in identifying the fungus in the lavage fluid. If these are negative, biopsy of the lung or other involved tissue is indicated. Skin testing and serologic tests are not reliable, and blood cultures usually do not demonstrate *B. dermatitidis*.

An aggressive approach to diagnosis is very much needed as ARDS caused by blastomycosis has a mortality rate of 50% to 68%. Survival depends on rapid diagnosis and aggressive therapy. In the previously referred case series of 10 patients, the average duration of illness before hospitalization was 25 days (range, 4-90 days) and average time to diagnosis from initial hospitalization was 8 days. All 5 patients who died had comorbidities, compared to 2 patients who survived. All survivors received a total dose of 2-3 g of amphotericin B.⁴

Although itraconazole is the drug of choice in most cases of blastomycosis, intravenous amphotericin is indicated for life-threatening infection. The dose should be rapidly escalated to reach a high maintenance dose of 0.7-1.0 mg/kg within 24 to 48 hours. A total dose of 2 g is the goal for a full course of therapy.⁶ This drug is associated with high degree of toxicity. Almost 75% of patients experience a decline in renal function. Liposomal amphotericin has less renal toxicity but no other proven therapeutic advantage over amphotericin B. Serum creatinine should be monitored biweekly and drug should be withheld for 48 hours if it goes above 2.5 mg/dl. Other side effects include anemia, anorexia and nausea, fever, hypokalemia and thrombophlebitis.⁶ Blood counts should be monitored at least once weekly and electrolytes twice weekly. Volume repletion with intravenous normal saline is recommended before and after amphotericin infusion. Phlebitis is avoided by frequent changes of peripheral catheters or by use of a central venous site. Premedication with aspirin or diphenhydramine may decrease the fever and chills.

CONCLUSION

Clinicians practicing in this endemic area for blastomycosis should be aware of this rare presentation of blastomycosis and its clinical and radiographic features. Blastomycosis should be included in the differential diagnosis of severe community acquired pneumonia. Early diagnosis is most important in this potentially lethal form of the disease. Microscopic examination of sputum for the characteristic yeast forms of the fungus is the most important test as it is simple, inexpensive and has a high diagnostic yield. If sputum is unavailable or nondiagnostic, invasive diagnostic procedures such as bronchoscopy should be performed immediately. The timing of bronchoscopy is important and referral to a facility where bronchoscopy is available should be considered early in the course of progressive pneumonia.

Amphotericin B is the drug of choice and treatment should be started without delay.

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