Blastomycosis: A Case Study of a Dimorphic Fungal Disease

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A 17-year-old male presented to a local hospital with symptoms of pneumonia and a hacking cough productive of yellow sputum. Direct examination of a bronchial lavage sample revealed organisms morphologically consistent with *Blastomyces dermatitidis*, which was confirmed by culture. The patient was placed on intravenous antifungal therapy and his condition improved dramatically.

OBJECTIVES: to describe the gross and microscopic morphologies of both yeast and mold forms of *B. dermatitidis*; to identify *B. dermatitidis* given patient history, and microscopic and colony morphology; to describe the symptoms of primary pulmonary infections caused by *B. dermatitidis*, and to name additional tissues typically affected by the systemic pathogen.

ABBREVIATIONS: AIDS = acquired immunodeficiency syndrome; ANA = antinuclear antibodies; HSV = herpes simplex virus; KOH = potassium hydroxide; RBC = red blood cell; WBC = white blood cell.

INDEX TERMS: blastomycosis; *Blastomyces dermatitidis*; dimorphic fungal disease; systemic fungi.

Clin Lab Sci 2004;17(3):145

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A 17-year-old male presented to a large medical center with a three-week history of fever, malaise, and shortness of breath with a hacking cough productive of yellow sputum. He stated that he had been diagnosed with bacterial pneumonia by another local medical facility ten days previously. His symptoms persisted during this time despite a course of outpatient antibiotics. Laboratory results on admission are depicted in Table 1.

Table 1. Laboratory results

Patient's tests	Results	Reference ranges
RBC count	4.7	4.5 – 5.3 x 10^{12}/L
Hemoglobin	139	130 – 160 g/L
Hematocrit	0.42	0.37 – 0.49
Platelet count	451	150 – 450 x 10^{9}/L
WBC count	19.6	4.5 – 13.5 x 10^{9}/L
WBC differential		
Neutrophils	0.89	0.40 – 0.70
Lymphocytes	0.06	0.15 – 0.45
Monocytes	0.00	0.01 – 0.08
Eosinophils	0.01	0.00 – 0.06
Erythrocyte sedimentation rate	98	0 – 10 mm/h
HIV antibody	Negative	Negative
Antinuclear antibodies	Negative	Negative
Blood cultures (6 sets)	No growth (5 days)	No growth (5 days)

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Two sputum collections from the patient failed to produce an acceptable specimen for culture. A bronchial lavage was performed when his clinical picture showed little improvement following a week of antibiotic therapy in the hospital. The resulting specimen yielded light growth of normal oropharyngeal flora and no acid-fast bacilli, *Mycoplasma* sp., *Legionella* sp., or viruses. Many broad-based budding yeast cells were seen on a fluorescent potassium hydroxide (KOH) combined with calcofluor white preparation of the bronchial lavage. After three days of proper incubation, fungal culture revealed heavy growth of a broad-based budding yeast identified as *B. dermatitidis*, confirming the disease etiology as pulmonary blastomycosis.

BLASTOMYCOSIS: A DIMORPHIC FUNGAL DISEASE

The disease blastomycosis was first characterized in the 1890s by Dr T Caspar Gilchrist.[1] He described a patient with disfiguring skin lesions originally attributed to tuberculosis, though yeast and not tubercle bacilli were present in a biopsy. The organism grew as a mold in culture when incubated at 25 °C to 30 °C, while inoculation with affected tissue led to the development of similar yeast-containing lesions in animals. Dr Gilchrist morphologically differentiated the yeast form of *Blastomyces dermatitidis* from *Candid*a sp. through its broad-based budding and large size.[2]

B. dermatitidis is categorized as one of the true systemic fungal pathogens. It is a dimorphic organism that grows as yeast or spherule forms in humans and culture at 37 °C, while producing a mold form in the external environment and culture at 25 °C to 30 °C. The fungus is capable of causing disseminated infection in immunocompetent hosts and is endemic to distinct geographic regions. In the United States, blastomycosis is mainly distributed throughout the Mississippi, Missouri, and Ohio River valleys in addition to North Carolina and the Great Lakes states. Canada, Africa, and the Middle East are also endemic zones for the fungus. *Blastomyces* sp. has been recovered from soil and other natural environments, but correlation between environmental exposure and development of disease is often difficult. Specific conditions support the organism's growth, including high temperatures and moist or wet soil enhanced by decaying vegetation. Other dimorphic fungal organisms include *Histoplasma capsulatum*, *Coccidioides immitis*, and *Paracoccidioides brasiliensis*.

PATHOGENESIS

Humans typically contract *B. dermatitidis* by inhaling infectious conidia in the environment. Direct cutaneous inoculation is an infrequent source of disease and may result from an animal bite or improper handling of clinical samples or cultures that contain the organism. Like other systemic mycoses, the infection is most prevalent in middle-aged men. This finding presumably correlates to their greater occupational and recreational exposure to soil.[3] Upon inhalation, *Blastomyces* conidia are transported to the lungs, where they convert to yeast forms and elicit an acute inflammatory reaction. During this primary phase, fungal dissemination may occur through the bloodstream and lymphatics. The cellular immune response typically produces granulomas in affected areas of the bronchopulmonary tree.[4] Blastomycosis develops after an incubation period of 30 to 45 days, although it is speculated that at least 50% of infected individuals remain asymptomatic.[5]

In contrast to the clinical picture seen with the majority of fungal infections, most patients with blastomycosis are healthy with no history of immunosuppression. For this reason, *Blastomyces* is not considered an opportunistic pathogen, even though the infection appears more likely to disseminate and prove fatal in immunodeficient patients. In a study of 100 cases of pulmonary blastomycosis, four of 84 immunocompetent patients and three of 16 immunocompromised patients died of the disease.[4]

CLINICAL PRESENTATION

Patients with blastomycosis have pulmonary disease of some severity. Since the disease has an indolent onset, many patients cannot pinpoint the time their symptoms began and may recall only a flu like illness. Most lack a history of acute pneumonia although specific pulmonary symptoms such as chest pain, shortness of breath, and cough become evident as the disease progresses. Coughing may be productive or nonproductive of sputum. Other common symptoms include weight loss, fever, and shortness of breath.[6]

Disseminated disease has been identified in up to 25% to 40% of patients with pulmonary blastomycosis.[5] The skin is most commonly affected, and patients may present with cutaneous lesions while lacking clinically evident pulmonary disease. Ulcerative bone lesions and involvement of the male reproductive system are also frequent complications of disseminated blastomycosis. Central nervous system infection is unusual but occurs in as many as 40% of AIDS patients. Such involvement results in meningitis or neurological lesions.

LABORATORY ROLE IN DIAGNOSIS

Patients with pulmonary blastomycosis are often initially assumed to have bacterial pneumonia, as clinical and radiologic

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findings in both diseases may be identical. In these cases, comprehensive evaluation of an appropriate specimen is essential in determining disease etiology. The presence of broad-based budding yeast in a respiratory sample or tissue supports a presumptive diagnosis of blastomycosis. Yeasts may be visualized by treating a sample with 10% KOH to dissolve excess purulent material and/or using the fluorescent compound calcofluor white to highlight fungal elements. Stained cytologic and histologic preparations can reveal similar information.

Definitive diagnosis requires culture isolation of *B. dermatitidis* from a clinical specimen. In culture at 25 °C to 30 °C, the slow to moderately rapid-growing mold phase produces variable macroscopic morphology. Colonies grown on Sabouraud dextrose agar may be white, tan, or brown and fluffy, or glabrous. Raised areas called spicules or prickles are sometimes visible in the colony centers. Microscopically, the fungus produces solitary oval to dumbbell-shaped conidia on short, unbranched conidiophores lateral to septate hyphae (Figure 1).

Conversion of the mold phase to yeast cells requires an enriched media such as brain-heart infusion with blood agar and an incubation temperature of 37 °C. Production of large, refractile, broad-based budding yeast cells in 37 °C (Figure 2) culture in conjunction with characteristic mold morphology at 25 °C to 30 °C is sufficient evidence to identify an isolate as *B. dermatitidis* (Figure 2). Identification can also be performed using immunodiffusion testing, which detects an exoantigen (A) produced by the mold phase of the organism.[3] Serological tests such as complement fixation (CF), immunodiffusion (ID), and enzyme immunoassay (EIA) can be used in evaluating patients for blastomycosis. Sensitivity varies among these tests from 57% to 62% for CF, 52% to 79% for ID, and 80% to 100% for EIA.[6]

Hematologic testing plays a secondary role in the diagnosis and management of patients with blastomycosis. An elevated white blood cell count with increased neutrophils and immature granulocytes is typically seen with fungal infections such as blastomycosis. An erythrocyte sedimentation rate may be highly elevated because of the disease's inflammatory component. Other laboratory values such as serum chemistry findings are usually of little diagnostic value.

TREATMENT

In the past, blastomycosis was considered a chronic, progressive disease in which the mortality rate approached 90%. Advances in antifungal therapy have lowered this figure to less than 10%, with patients suffering from overwhelming disease in conjunction with respiratory failure making up the majority of blastomycosis-related deaths.[5] Until recently, intravenous amphotericin B was the standard treatment for blastomycosis. It remains a firstline agent for life-threatening infection as well as the immunocompromised, pregnant patients, and children. Being less toxic than amphotericin B, ketoconazole and itraconazole are the preferred treatments in non-life-threatening cases of blastomycosis and as maintenance therapy for patients who have completed a course of amphotericin B.

Figure 1. Blastomyces dermatitidis — conidia found in the mold form.

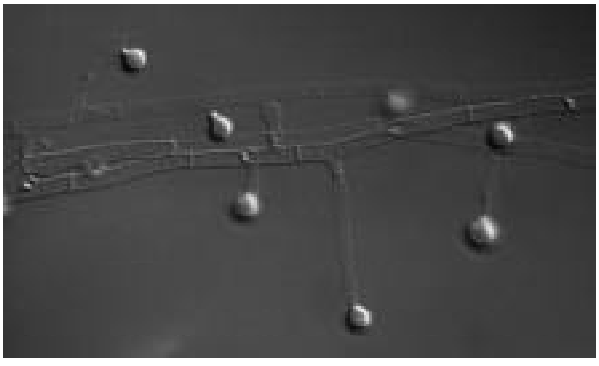

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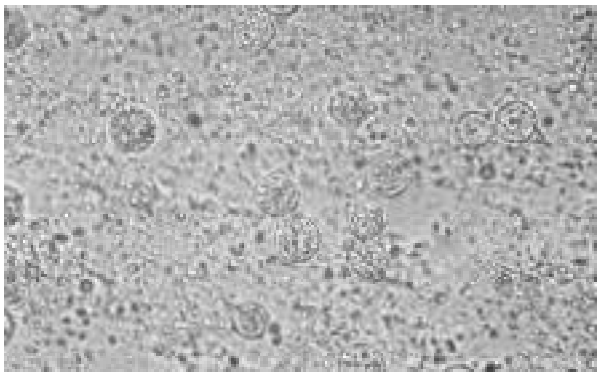
Figure 2. Blastomyces dermatitidis — thick-walled, budding yeast form.



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The goal of therapy is to eliminate the symptoms of the disease as well as the organisms. Unfortunately, total eradication is often impossible in immunodeficient patients, who may require chronic suppressive therapy with an azole. Conversely, spontaneous cure in the absence of therapy has been documented in a number of patients with acute pulmonary blastomycosis.[5] These cases have led some experts to suggest that therapy may be withheld in favor of close monitoring for otherwise healthy patients.

CASE CONCLUSION

This patient presented with a clinical picture consistent with bacterial pneumonia. His elevated white blood cell count and increased neutrophils were indicative of ongoing infection, despite repeatedly negative blood cultures. His highly elevated erythrocyte sedimentation rate implied an inflammatory process. A negative human immunodeficiency virus (HIV) antibody screen and antinuclear antibodies (ANA) connoted that an immunodeficient or autoimmune condition was highly unlikely for the patient's symptoms. A number of infectious agents were suggested against by negative urinary pneumococcal and *Legionella* antigens in addition to negative *Coxiella burnetii*, *Clamydia pneumoniae/psittaci*, *Francisella tularensis*, *Mycoplasma*, *Erlichia*, Cocksackie B, and herpes simplex virus (HSV) antibodies. After one week of extensive antibiotic therapy, the patient's condition failed to improve, and a bronchial lavage was obtained to assist in diagnosis. A routine bacterial culture performed on the specimen produced no significant isolates, while acid-fast, *Mycoplasma* sp., *Legionella* sp., and viral cultures were negative. Direct examination of the sample for fungal elements revealed organisms morphologically consistent with *B. dermatitidis*, a finding later confirmed by culture isolation.

Following identification of *B. dermatitidis* as the causative agent of the patient's illness, a bone marrow aspiration and biopsy were performed to rule out disseminated blastomycosis. Routine bacterial, acid-fast bacillus, and fungal cultures of the aspirate were negative. The patient was placed on intravenous antifungal therapy with amphotericin B, at which point his condition began to improve steadily. Upon further questioning about the possible origin of his illness, the patient stated that he had spent weekends at his grandfather's house, which had been flooded during a hurricane the previous year. He recalled using a wheelbarrow to transport remaining mud, rotting leaves, and other debris from the house. These activities were the most likely source of the patient's infection. After a three-week hospital stay, the patient was discharged in good condition with itraconazole as maintenance therapy.

SUMMARY

This article illustrates a typical case of pulmonary blastomycosis, which is caused by the dimorphic fungal pathogen *B. dermatitidis*. The organism may cause both pulmonary and extrapulmonary disease and is typically contracted through inhalation of infectious conidia found in the environment. Diagnosis and effective treatment of pulmonary blastomycosis is dependent on the isolation and successful identification of *B. dermatitidis* from a clinical sample.

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