

Severe acute respiratory distress syndrome in a liver transplant patient

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ABSTRACT

This case report presents a 46-year old man with a failed liver transplant who presented with malaise and dyspnea. Imaging studies revealed diffuse reticulonodular infiltrates and innumerable miliary nodules and a left upper lobe consolidative mass. Examination of bronchoalveolar lavage fluid demonstrated yeast cells with broad-based budding. He was diagnosed with pulmonary blastomycosis and started therapy with liposomal amphotericin. In spite of therapy, he clinically worsened, developing acute respiratory distress syndrome (ARDS) and eventually expired.

1. Introduction

Blastomycosis is granulomatous infection caused by the dimorphic fungus, *Blastomyces dermatitidis*, an organism that is endemic to the United States, particularly the upper Midwest and south central US as well as regions that border the Great Lakes and St. Lawrence seaway [1]. It grows in two forms, exhibiting the mycelial (mold) phase at room temperature and as a yeast at 37 °C. Infection with the organism is caused by inhalation of conidia, which then convert to the yeast phase in tissue. In immunocompetent individuals, infections can be sub-clinical and, therefore, the true incidence of disease may be underestimated. In one case series among 11 solid organ transplant patients, 78% of patients with pulmonary disease developed severe respiratory failure with 67% of those progressing to ARDS [2]. The mortality of uncomplicated pulmonary blastomycosis is low but in the setting of severe pneumonia and ARDS mortality exceeds 50–70% [3].

Solid organ transplant recipients are at increased risk for developing severe infections due to the use of immunosuppressive agents to reduce allograft rejection. Risk of infection following a transplant is often due to two factors: epidemiologic exposure to the organism and the state of immunosuppression of the host [4]. In spite of the advances in transplant medicine, morbidity and mortality due to infectious complications continues to be a significant problem, with infections fungal organisms implicated in 22% of post-transplant infections in one study [5].

2. Case

A 46 year old male landscaper with alcoholic cirrhosis status-post

orthotopic liver transplant 15 months ago, on maintenance tacrolimus and mycophenolate, was admitted with a 5-day history of malaise and dyspnea. It was noted that during his initial hospitalization for his transplant, the patient was found to have enlarged mediastinal lymph nodes and axillary lymphadenopathy and was empirically started on itraconazole due to concern for *Histoplasma capsulatum*. Histoplasma antigen testing and serology were negative, and itraconazole therapy was stopped after 3 months. One month prior to his current admission he was treated for biopsy-proven acute cellular rejection, presumed secondary to calcineurin inhibitor non-compliance. He received 3 doses of thymoglobulin (2 mg/kg) and 3 doses of methylprednisolone (500 mg). At that time trimethoprim-sulfamethoxazole and valganciclovir were added for *Pneumocystis jirovecii* and human cytomegalovirus prophylaxis, respectively.

On this admission (day 0) he was directly admitted to our surgical intensive care unit from an outside hospital. He was admitted to the OSH for severe anemia (Hgb 4.8 g/dL) and was transfused with two units of pRBCs. Upon admission to our SICU, he was afebrile with normal oxygen saturation; laboratory studies revealed a normal white blood cell count (5880/mm³), anemia with a hemoglobin of 9.0 g/dL, acute kidney injury (creatinine 2.4 mg/dL, baseline 1.2 mg/dL) and an elevated tacrolimus level (24 ng/mL).

On hospital day 1, he appeared stable and was transferred out of the ICU to a general medical floor. An infectious disease consultation was sought for concern of infectious anemia in a post-transplant patient. On hospital day 2, the patient subjectively felt worse; he developed fever to 38.6 °C; a portable chest radiography showed diffuse reticulonodular infiltrates. A CT of the chest was obtained, and showed innumerable miliary nodules and a 3 × 6 cm left upper lobe (LUL) consolidative

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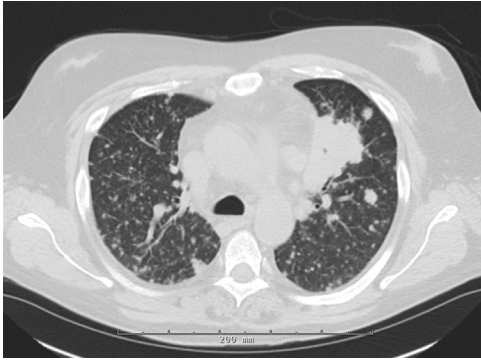


Fig. 1. Chest CT demonstrating extensive miliary nodules throughout both lungs along with scattered solid nodules and consolidative opacity with central cavitation in the left upper lobe.

mass with mediastinal adenopathy (Fig. 1).

Blood cultures were drawn, but there was no growth of any pathogen. He was begun on empiric cefepime and liposomal amphotericin B (3 mg/kg/day). He was transferred back to the SICU for increasing respiratory distress. On hospital day 3, a bronchoscopy with transbronchial biopsy was performed. Initial pathology findings of the LUL transbronchial biopsy specimen stained with Periodic acid-Schiff (Fig. 2) and Gömöri methenamine silver stain (Fig. 3) are shown, which revealed clusters of benign bronchial cells and numerous alveolar macrophages. In addition, numerous cells consistent with fungal organisms were seen and confirmed by PAS and GMS staining. The yeast forms observed were consistent with *Blastomyces dermatitidis* (Figs. 2 and 3). The typical morphologic findings include the characteristic thick-walled refractile cell with broad-based budding.

Additional testing, including immunohistochemical staining for CMV and HSV were negative; AFB and Fites stains were negative for mycobacteria. A urine *Histoplasma* antigen was sent; the result of 12.99 mg/dL came back on hospital day 4. Based on the clinical and microbiologic findings, a diagnosis of severe pulmonary blastomycosis was made. He developed worsening hypoxic respiratory failure with acute respiratory distress syndrome (ARDS) on day 5, requiring endotracheal intubation and full mechanical ventilator support. Liposomal amphotericin B dose was increased (5 mg/kg/day) and high dose solumedrol (60 mg every 6 h) was added. The patient was placed on extracorporeal membrane oxygenation (ECMO) and began hemodialysis for severe acidosis; pressor support was maximal. Given his poor prognosis, the patient's family withdrew care, and on hospital day 6 he died.

Five days following the bronchoscopy, his bronchial washing culture grew a white mold on Sabouraud dextrose agar (Remel, Lenexa, KS), with macroscopic and microscopic morphology consistent with

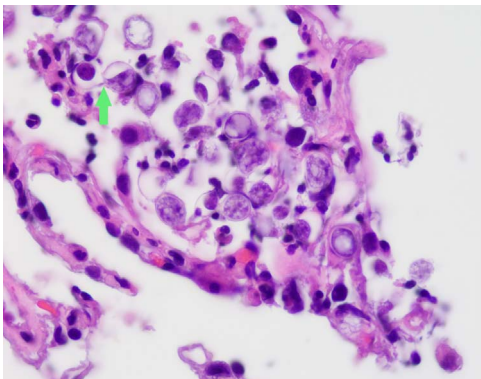


Fig. 2. Numerous thick walled, refractile yeast cells with characteristic broad-based budding (arrow) are seen in the transbronchial biopsy sample stained with PAS.

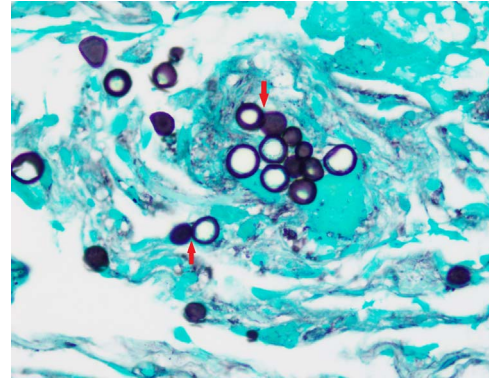


Fig. 3. GMS preparation of transbronchial biopsy sample with large cluster of yeast cells with two examples of broad based budding (arrows).

Blastomyces. DNA probe confirmation was performed using the AccuProbe *Blastomyces dermatitidis* culture identification test (GenProbe, San Diego, CA) and was positive.

3. Discussion

Blastomyces dermatitidis is a dimorphic fungus that most often causes asymptomatic pulmonary disease. While pulmonary infections are most common, the organism can disseminate throughout the body, leading to infections in the skin, bones and genitourinary system. Direct skin inoculation is uncommon, but can occur, which often results in lymphadenitis, that is not seen in cutaneous disease due to dissemination. It is most often diagnosed in patients in North America, but cases have been reported worldwide.

This report describes an acute case of pulmonary blastomycosis in an immunocompromised host diagnosed with biopsy-proven liver allograft rejection. Notably, this patient had multiple risk factors that put him at risk for developing a severe infection following his transplant, including environmental exposure due to living in a region in which *B. dermatitidis* is endemic and lack of adherence to his prescribed immunosuppressive regimen. The patient was employed as a groundskeeper and maintenance worker, affording opportunity for occupational exposure to organisms within the soil. Initially it was thought that the patient's severe anemia could be due to infection with parvovirus B19, but the significant increase in hemoglobin following transfusion and other clinical findings made that less likely.

Diagnosis of blastomycosis may often be delayed due to failure to consider this agent. Culture remains the gold standard for definitive diagnosis of infections caused by *B. dermatitidis* [6]. In patients with a high burden of disease, yeast cells may be seen in a direct Gram stain of sputum or bronchial washings or on histopathology/cytology, which demonstrate the characteristic broad-based budding yeast, which is enough to provide a presumptive diagnosis [7]. Presumptive findings may justify initiating antifungal therapy pending culture results. Diagnosis by serology is challenging and not routinely recommended due to poor analytic performance. Antigen testing has been widely adopted to presumptively identify an endemic fungal infection, including blastomycosis. Antigen testing from clinical specimens is imperfect, however, as there is strong cross-reactivity reported with other endemic fungi, most notably *H. capsulatum* [8], which was shown in this case.

For patients with severe pulmonary disease, a lipid formulation of amphotericin B (3–5 mg/kg/day) is recommended as first line therapy and administered for at least 1–2 weeks or until improvement is noted, followed by oral itraconazole for 6–12 months [9]. Other triazoles, such as voriconazole, posaconazole and isavuconazole, have been used successfully in some cases, though comparative clinical trials are lacking [10–12].

In summary, this case demonstrates the rapid progression of a case

of blastomycosis in an immunosuppressed patient. High clinical suspicion for this organism early on, can drastically affect the outcome if proper therapy is initiated quickly. In spite of this, our patient rapidly deteriorated and his hypoxemia progressed to ARDS. In spite of extraordinary measures, including full ventilator support, dialysis, and ECMO, the patient expired.

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Conflict of interest

There are no conflicts of interest.

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