Disseminated blastomycosis in coalworkers' pneumoconiosis

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ABSTRACT

Blastomyces dermatitidis is a thermally dimorphic fungus that can cause pulmonary, extrapulmonary, or disseminated infections. Though it can infect both immune-competent and immunocompromised hosts, the disease can be severe in immunocompromised hosts. Exposure to silica dust is associated with silicosis, and this is associated with impaired immunity and an increased risk of mycobacterial and fungal infections. The fungal infections commonly associated with pneumoconiosis are pulmonary aspergillosis, histoplasmosis, coccidioidomycosis, and cryptococcosis. However, there is a dearth of data on the association of pneumoconiosis and blastomycosis. Clinical deterioration and new cavitory lesions in patients with pneumoconiosis should alert clinicians of new pulmonary infection. Traditional sputum sampling may lead to poor diagnostic yield, because the organism is frequently surrounded by a fibrotic wall. Aggressive diagnostic testing with lung or skin biopsies may be warranted. We present the first reported case of disseminated blastomycosis in a patient with coalworkers' pneumoconiosis.

KEYWORDS Acute respiratory distress syndrome; blastomycosis; pneumoconiosis; progressive massive fibrosis; silicosis

Blastomycosis is a thermally dimorphic fungi endemic to the South Central, Southeastern, and Midwest regions of the USA.¹ The primary site of infection is the lungs, and it causes acute and chronic pneumonitis and, rarely, a fulminant pulmonary infection with acute respiratory distress syndrome. Infection can disseminate to extrapulmonary organs, especially skin. Although immune-competent and immunocompromised hosts can acquire the disease, the disease tends to be severe in immunocompromised hosts.^{2,3} Pneumoconiosis, especially silicosis, is associated with an increased risk of mycobacterial and fungal infection.^{4–6} We present a case of disseminated blastomycosis in a patient with coalworkers' pneumoconiosis.

CASE REPORT

A 58-year-old white man with coalworkers' pneumoconiosis who was being evaluated for lung transplantation presented with progressive cough, hemoptysis, fever, and night

sweats. His oxygen requirement increased from 4 to 6 L/min at rest and he had lost 15 pounds in the preceding 6 weeks. He had a 15 pack-per-year history of smoking but denied any illicit drug or alcohol use. He had not traveled outside the USA but had an uncle who had previously been diagnosed and successfully treated for tuberculosis.

His temperature was normal; heart rate, 100 beats/min; and respiratory rate, 16 breaths/min. His arterial saturation was normal on 6 L/min of oxygen via nasal cannula. Auscultation revealed bibasilar rhonchi. The right anterior thigh had a 1-cm nodule and a shallow ulcer with an exudative base measuring 2 cm in diameter (*Figure 1a*). He also had erythema extending from the dorsum of the right foot to above the right ankle (*Figure 1b*). He was started on broad-spectrum intravenous antibiotics for severe pneumonia. Blood and sputum cultures were obtained. Computed tomography (CT) of the chest showed a new left-sided cavity on previously known progressive massive fibrosis (*Figure 2*). On day 2 of admission, punch biopsies of the right thigh ulcer

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Figure 1. (a) Right anterior thigh nodule and ulcer. (b) Erythematous lesion of right foot.

Figure 2. CT images of the hilar area (left column) and base of the lungs (right column). CT chest images reveal the presence of progressive massive fibrosis bilaterally without cavitation and pulmonary infiltrates in the base 2 years prior to presentation (upper row), development of new cavitation in the lung mass on the left side without pulmonary infiltrates in the base 8 months prior to presentation (middle row), and persistent cavitation with new pulmonary infiltrates in the lung base bilaterally at the time of clinical presentation (lower row).

and nodule disclosed pseudoepitheliomatous hyperplasia with a surrounding superficial and deep dense granulomatous infiltrate composed of lymphocytes, histiocytes, and giant cells with background necrosis and hemorrhage. Periodic acid-Schiff and Gomori methenamine silver staining revealed occasional fungal organisms, some with broad-based budding, within the granulomatous infiltrate (Figure 3). Mucicarmine staining of the specimen was negative. Sputum culture revealed yeast but was otherwise unremarkable, and blood cultures remained negative. He was HIV negative and had normal CD4 counts. Gold QuantiFERON testing for tuberculosis was negative. Radiograph of the right foot did

Figure 3. Histopathology images. (a) Low-power image of the cutaneous ulcer demonstrating pseudoepitheliomatous hyperplasia with surrounding superficial and deep dense granulomatous infiltrate composed of lymphocytes, histiocytes, and giant cells with background necrosis and hemorrhage. There was an accompanying overlying parakeratosis, spongiosis, and acanthosis. (b) Gomori-methenamine silver staining revealed occasional fungal organisms, some with broad-based budding, within the granulomatous infiltrate (arrow).

not reveal any features of osteomyelitis. He had elevated serum galactomannan, urine *Histoplasma*, and *Blastomyces* antigen levels. On day 3, intravenous antibiotics were switched to cefazolin for nonpurulent cellulitis of the right leg, and intravenous amphotericin B was started. Fungal cultures from the punch biopsy later grew *Blastomyces dermatitidis*. Despite these measures, the patient developed acute respiratory distress syndrome requiring intubation and mechanical ventilation on day 13 of admission and died on day 15 due to a hypoxic cardiac arrest.

DISCUSSION

Our patient had a known diagnosis of coalworkers' pneumoconiosis with CT of the chest showing nodular consolidation and dense fibrosis extending to the periphery of the chest suggestive of progressive massive fibrosis. It also showed calcification indicative of silicosis.⁷ New pulmonary cavitation in progressive massive fibrosis with fever, hemoptysis, and weight loss was concerning for silico-tuberculosis.⁸

Silica dust exposure results in impairment of the immune system by direct inhibition of CD8+ T lymphocytes and impairment of phagocytic activity and viability of macrophages and neutrophils, with increased predisposition to fungal and mycobacterial infections.^{5,6} Additionally, chronic exposure to silica has been shown to cause decreased activity of T-helper cell 1, which releases cytokines such as interferon-gamma that lead to fungicidal activity in macrophages.^{9,10} The patient was HIV negative and tested negative for tuberculosis exposure.

Common fungal infections associated with pneumoconiosis include aspergillosis, histoplasmosis, coccidioidomycosis, and cryptococcosis.⁵ There is a dearth of data on the association of pneumoconiosis and blastomycosis. This patient's diagnosis of disseminated blastomycosis complicating pneumoconiosis is circumstantial in the absence of respiratory cultures or autopsy documenting *Blastomyces* infection. However, he had new-onset cavitation, which is usually the first indication of infection in pneumoconiosis.^{11,12} The lack of positive sputum cultures during this time could be explained by the pulmonary infection being "walled off"

inside the fibrosis. The diagnostic yield of traditional testing may be low fungal lung diseases. Aggressive testing with transcutaneous or transbronchial lung biopsy or any new skin lesions may be warranted.

Our patient had positive Galactomannan test for *Aspergillus* infection; however, this likely represents a cross-reaction with the *Blastomyces* antigen. The enzyme immunoassay uses a monoclonal antibody to detect the Galactomannan antigen and is known to cross-react with antigen epitopes on *Fusarium* species, *Penicillium* species, *Histoplasma capsulatum*, and *Blastomyces* species.^{13–15}

Patients with mild to moderate *Blastomyces* infection can be treated with azoles. Moderately severe to severe disease will need intravenous amphotericin B followed by itraconazole for step-down therapy. However, in patients with central nervous system involvement, voriconazole is the preferred step-down therapy. A prolonged course of 6 to 12 months of antifungal therapy is recommended.¹⁶

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