Fatal Cunninghamella berthollletiae Infection in an Immunocompetent Patient*

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The first fatal Cunninghamella berthollletiae infection in a clinically immunocompetent host is reported. This case differs from previously reported cases by the lack of extensive vascular invasion and thrombosis.

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Zygomycosis represents an acute and almost uniformly fatal systemic fungal infection caused by species of the class Zygomycetes. These systemic infections are classified as rhinocerebral, pulmonary, gastrointestinal, cutaneous, and widely disseminated. Four species are pathogenic in humans: Rhizopus, Absidia, Mucor, and Cunninghamella in order of decreasing frequency. Case reports have described zygomycosis only in immunocompromised patients or those with a chronic illness. Classic predisposing disorders include diabetes mellitus, malignancy, steroid and antimetabolite therapy, cirrhosis, organ transplantation, and malnutrition. Pathologic features are similar regardless of species. Typically, there is tissue and vascular wall invasion, with subsequent vascular thrombosis and tissue bed infarction.

Cunninghamella berthollletiae infection is extremely rare even though this fungus is ubiquitous in nature. Since the first report in a cancer patient in 1959, there have been 11 more cases confirmed in the literature. However, there are no documented zygomycotic infections in an immunocompetent host. We present the first reported case of C berthollletiae in a clinically immunocompetent patient.

CASE REPORT

A 61-year-old white man with a history of alcoholic binges, none recently, was admitted for progressive dyspnea, productive cough, night sweats, fevers with chills, and a 9.1 kg (20 lb) weight loss over the prior four months. He worked as a naval electrician with no asbestos, toxic, or chemical exposure and was treated for parotitis two and five months prior to admission. His only medication was a nasal mist (Primatine Mist).

Physical examination revealed an oral temperature of 38.3°C, respiratory rate 30 breaths per minute, accessory muscle usage, normal parotid glands and right sided bibasilar rales, scattered rhonchi and wheezes. A three component friction rub was present.

Hemoglobin value was 10 g/dl; WBC count, 18,000 cells/µm (55 percent neutrophils, 17 percent bands, 16 percent lymphocytes, 8 percent monocytes); and normal results from renal and liver function studies. Serum albumin was 3.2 g/dl. Chest roentgenogram showed a right pleural based mass, a pleural effusion, pneumothorax, and bilateral interstitial markings.

An exudative, bloody pleural effusion was drained by insertion of a chest tube (Fig 1). Purified protein derivative was negative and mumps and Candida skin test results were positive. Preliminary sputum cultures, although reported as growing a Rhizopus species, were interpreted as a laboratory contaminant. Pleural fluid, bronchial washings, and sputum grew C berthollletiae. Amphotericin B, 30 mg/day, was instituted, but the patient’s oxygenation deteriorated, and on the 19th hospital day, he suffered a cardiorespiratory arrest and died.

Post-mortem examination revealed a right upper lobe cavitary lesion, a right pleural effusion, right sided fibrous pericarditis, and pleuritis. There was no evidence of a malignancy. Abscess wall and surrounding lung parenchyma sections (stained with Gomori methenamine silver) revealed hyphal fragments with budding conidiophores (Fig 2).

Isolates were confirmed as C berthollletiae by the Centers for Disease Control in Atlanta. A zygomycosis serum ELISA antibody titer was 1:12,800. The fungus was not recovered from the blood or from antemortem bone marrow cultures. Microscopy preparations from the cavitary lesion showed fungal elements characteristic of Cunninghamella species (Fig 3). In vitro susceptibility tests revealed the minimum inhibitory concentration of amphotericin B was 25 µg/ml; the minimum fungicidal concentration was greater than 100 µg/ml. Thus, this isolate was unusually resistant to amphotericin B.

DISCUSSION

Inhalation of airborne asexual sporangiophores is felt to

\[ \text{Figure 1. Persistent right pneumothorax, an upper lobe mass (cavity) and diffuse interstitial disease.} \]

\[ \text{Figure 2. Histologic section of lung tissue showing invasion by Cunninghamella berthollletiae hyphal fragment with budding conidiophore. Methenamine silver stain original magnification } \times 200. \]

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be the mechanism of fungal transmission, although rarely the organisms can proliferate in skin breaks or pass through intact mucous membranes. Alveolar macrophages, the first line of defense, inhibit fungal spore germination and hyphal growth and prevent tissue invasion. Inhibition of macrophage function (ie, cortisone therapy, iron overload) may allow fungal spore germination, proliferation, and subsequent tissue invasion.\(^3,^{11,12}\) The previous cases of *C. bertholletiae* have been reported in patients with underlying diseases associated with compromised host defenses.\(^1\) All patients except one had classic tissue invasion, with subsequent blood vessel invasion and destruction of the perfused area.

In contrast, our patient was clinically immunocompetent as evidenced by an elevated white blood cell count with a lefward shift, functioning cell-mediated immunity reflected by the positive response to control skin testing antigens, normal serum albumin and iron levels, a negative ELISA for human immunodeficiency virus, no prior history of repeated pulmonary infections, and no clinical evidence of malnutrition. However, specific leukocyte function studies (phagocytosis, chemotaxis, oxidative burst, lysozymal enzyme function) were not tested.

Our case has the following unusual features: (1) the significance of the recurrent parotid infections is unclear and this organ could have been the primary site of infection; (2) the original positive *C. bertholletiae* cultures were discounted as laboratory contaminants, thus delaying early treatment. Only after the organism was isolated from multiple specimens was it realized that *C. bertholletiae* was the pathologic agent in our patient's illness; and (3) our patient did not display the typical tissue and blood vessel invasion seen with zygomycosis. One other reported case describing limited tissue invasion was in a patient with thalassemia complicated by iron overload, neutropenia, and splenectomy.* We hypothesize that this lack of vascular involvement and dissemination was secondary to a relatively intact immune system which attenuated but could not eradicate the infection. Although our patient had an apparent clinically intact immune system, we cannot rule out local pulmonary immune deficiency or a diffuse subclinical deficiency.

In summary, *C. bertholletiae* represents a true pathogenic fungal species. We report the first case of pulmonary infection in a patient with an apparent competent immune system. *C. bertholletiae* should be regarded as a true pathogen even in nonimmunocompromised patients if positive cultures are reported. Zygomycosis can occur without evidence of thrombosis. Effective therapy usually involves surgical debridement and the administration of systemic antifungal agents.

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