Cluster of Pulmonary Infections Caused by *Cunninghamella bertholletiae* in Immunocompromised Patients

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*Cunninghamella bertholletiae* is a rare cause of pulmonary mucormycosis. We describe a cluster of invasive pulmonary infections caused by *C. bertholletiae* in 4 immunocompromised patients that occurred during a 2-year period at 1 center. Three of the patients were receiving antifungal prophylaxis with itraconazole. Presenting symptoms were fever unresponsive to antibacterial chemotherapy, hemoptysis, and infiltrates on chest radiograms. Three patients were treated with liposomal amphotericin B. Only 1 patient survived.

Invasive fungal infections are serious and often fatal complications in immunocompromised patients. *Candida* species, *Aspergillus* species, and *Cryptococcus neoformans* are the most frequent pathogens of these infections [1, 2]. Similar conditions caused by other fungal pathogens such as *Trichosporon beigeli*, *Fusarium* species, and *Penicillium marneffei* have been described, and these pathogens are being isolated with increasing frequency [3, 4].

*Cunninghamella bertholletiae* (class Zygomycetes, order Mucorales) is a saprophytic, ubiquitous fungus that is found in soil. It is rarely isolated as an agent of zygomycoses in immunocompromised patients [5]. We reviewed the medical records of 4 immunocompromised patients who developed serious pulmonary infections caused by *C. bertholletiae* during a 2-year period at the University Hospital in Frankfurt, Germany; we describe this cluster of infections here (table 1).

Case Reports

**Case 1.** A 60-year-old woman in first complete remission of acute lymphoblastic leukemia was admitted to our hospital in November 1998 for consolidation therapy with cytarabine and teniposide (German ALL [acute lymphoblastic leukemia] Study Group protocol) [6]. Eight days after the start of chemotherapy, she developed neutropenia (absolute neutrophil count, <500/mL). She developed fever and abdominal pain 1 day later. CT of the abdomen revealed evidence of appendicitis and cholecystitis. Cholecystectomy and appendectomy were performed the same day. Both diagnoses were confirmed histopathologically. There was no evidence of invasive fungal infection of the gallbladder or appendix. The bone marrow regenerated after 14 days of neutropenia, and the patient developed mild hemoptysis. The platelet count, prothrombin time, and partial thromboplastin time were normal. A CT scan of the chest showed a homogenous alveolar opacification in the left upper and right lower lobes. Treatment was not started.

Follow-up CT performed 7 days later showed decreasing infiltrates, and the patient was discharged from the hospital 4 weeks thereafter in stable condition. Four days later, the patient developed massive hemoptysis and was readmitted. A CT scan of the chest revealed multiple cavities in both lower lobes and left middle and upper lobes. Antifungal therapy with amphotericin B (1 mg/kg/day) was started on the same day. Bronchoscopy was done; this procedure revealed hemorrhage of the right lower lobe and a mass obstructing the left upper bronchus. Analysis of bronchial aspirates (BAs) revealed broad, nonseptate hyphae. Cultures revealed a fast-growing hyphomycete that was identified as *C. bertholletiae*. Therapy was changed to liposomal amphotericin B (6 mg/kg/day) at that time. However, her respiratory status worsened rapidly, and she died. Autopsy was not performed.

**Case 2.** A 51-year-old man received induction therapy with daunorubicin, vincristine, L-asparaginase, and prednisone for newly diagnosed acute lymphoblastic leukemia in July 1998. Ten days after onset of neutropenia, the patient developed fever and palpitations. Electrocardiography revealed new onset atrial fibrillation. Chest radiography showed a ground glass opacification in the left lung that was interpreted as pulmonary hemorrhage. Bronchoscopy was performed 1 day later; this procedure showed signs of acute bronchitis and bleeding. Treatment with liposomal amphotericin B (3 mg/kg/day) was started. Microscopy of bronchoalveolar lavage (BAL) fluid showed broad, nonseptate hyphae. *C. bertholletiae* was isolated from BAs and BAL fluid. The isolate was resistant to flucytosine (MIC, >128 μg/mL; ATB Fungus, bioMérieux, Lyon, France) and itraconazole (MIC, >1 μg/mL; MIC determined...
Table 1. Characteristics, clinical presentation, antifungal treatment, and outcome for 4 patients with Cunningramella bertholletiae pulmonary infections that occurred during a 2-year period at 1 center.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age in years, sex</th>
<th>Underlying condition</th>
<th>Neutropenia, days</th>
<th>Itraconazole prophylaxis</th>
<th>Clinical presentation</th>
<th>Antifungal therapy (maximum daily dose; total dose)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60, F</td>
<td>ALL</td>
<td>14</td>
<td>Yes</td>
<td>Pulmonary hemorrhage</td>
<td>AmB (1 mg/kg; 780 mg)</td>
<td>Died</td>
</tr>
<tr>
<td>2</td>
<td>51, M</td>
<td>ALL</td>
<td>12</td>
<td>Yes</td>
<td>Fever, palpitations, pulmonary hemorrhage</td>
<td>Liposomal AmB (4 mg/kg; 3.05 g)</td>
<td>Died</td>
</tr>
<tr>
<td>3</td>
<td>61, F</td>
<td>Renal TX</td>
<td>0</td>
<td>No</td>
<td>Progressive respiratory distress after treatment of PCP</td>
<td>Liposomal AmB (6 mg/kg; 12.9 g); 5-FC (42.5 g 4 times daily)</td>
<td>Died</td>
</tr>
<tr>
<td>4</td>
<td>55, M</td>
<td>NHL</td>
<td>8</td>
<td>Yes</td>
<td>Fever, chest pain, blood-timed sputum</td>
<td>Liposomal AmB (6 mg/kg; 4.8 g)</td>
<td>Cured</td>
</tr>
</tbody>
</table>

NOTE: ALL, acute lymphoblastic leukemia; AmB, amphotericin B; F, female; M, male; NHL, non-Hodgkin’s lymphoma; PCP, Pneumocystis carinii pneumonia; TX, transplantation; 5-FC, flucytosine.

by a microdilution assay [7]) but was susceptible to amphotericin B (MIC, <1 μg/mL; ATB Fungus).

The dosage of liposomal amphotericin B was increased to 4 mg/kg/day. Fever resolved after bone marrow regeneration 12 days after onset of neutropenia, but chest radiographs showed progressive infiltrates. The patient died of massive pulmonary hemorrhage after treatment for 13 days. The platelet counts, prothombin time, and partial thromboplastin time were normal before the hemorrhage occurred. Postmortem examination showed multiple cavities in both lungs that contained sequestered lung tissue. Microscopic examination of the sequestered lung tissue showed ischemic necrosis and fungal hyphae invading small blood vessels. No other organs were involved.

Case 3. A 61-year-old female was admitted to the hospital because of pneumonia in October 1998. She had received a cadaveric renal transplant because of end stage polycystic kidney disease 6 months earlier. Vascular rejection had been managed with plasmapheresis and administration of methylprednisolone, tacrolimus, mycophenolate, and basiliximab. At the time of admission, chest radiography revealed a left lower lobe patchy infiltrate and a diffuse interstitial pattern. Results of laboratory testing were unremarkable except for lymphopenia (CD4 lymphocyte count, 79 cells/μL; CD8 lymphocyte count, 40 cells/μL). Bronchoscopy was performed. Grocott-Gomori methenamine–silver nitrate staining of BAL fluid revealed *Cunningramella bertholletiae* cysts. Treatment with iv trimethoprim-sulfamethoxazole, erythromycin, and ganciclovir was initiated. Immunosuppressive therapy was reduced to prednisolone. The patchy infiltrates resolved, but the diffuse interstitial infiltrates progressed.

Eight days after admission, mechanical ventilation was started because of progressive respiratory insufficiency. Bronchoscopy was performed again; this procedure showed acute bronchitis and occlusion of the right bronchial tree by a fibrinous mass. Analysis of BAL fluid was negative for *Pneumocystis* but revealed broad, nonseptate hyphae. Cultures of BAs and subsequent endotracheal aspirates yielded *C. bertholletiae*. Therapy with amphotericin B (1 mg/kg/day) and flucytosine (2.5 g 4 times daily) was initiated. When culture results became available, treatment was changed to liposomal amphotericin B (6 mg/kg/day) and nebulized amphotericin B (80 mg twice a day). A CT scan of the chest showed a diffuse ground glass infiltrate, a pleura-based homogenous consolidation, and cavities. Her condition deteriorated despite high doses of antifungal therapy, and she died 2 months after admission. Autopsy was not performed.

Case 4. A 55-year-old man was referred to our hospital because of a relapse of stage IVB T cell lymphoma in June 1997. He was treated with dexamethasone, melphalan, etoposide, cytarabine, Carmustine, and granulocyte colony-stimulating factor. On the second day of neutropenia, the patient developed intermittent fever (temperature to 38.4°C), pleuric chest pain, and blood-timed sputum. Fever was unresponsive to broad-spectrum antibacterial therapy. Chest radiography revealed bilateral, pleura-based, ill-defined, rounded densities. Bronchoscopy was unremarkable. Grocott-Gomori methenamine–silver nitrate staining of BAs revealed broad, nonseptate hyphae. *C. bertholletiae* was isolated from BAs and subsequent sputum specimens. In vitro susceptibility testing showed that the isolate was resistant to flucytosine (MIC, >128 μg/mL) and itraconazole (MIC, >1 μg/mL) but was susceptible to amphotericin B (MIC, <1 μg/mL).

Antifungal treatment with amphotericin B (1 mg/kg/day) was initiated 2 days after the onset of fever. With resolution of neutropenia after 8 days, fever abated, and administration of granulocyte colony-stimulating factor was stopped. Concomitant treatment with 150 μg of granulocyte-macrophage colony-stimulating factor was administered for 8 days. Therapy was changed to liposomal amphotericin B (3 mg/kg/day) after the patient developed infusion-related side effects after 9 days of conventional amphotericin B treatment. The dosage of liposomal amphotericin B was increased to 6 mg/kg/day because the patient’s condition worsened further. A follow-up chest radiogram 6 days later revealed that the pulmonary infiltrates were resolving.

Treatment was continued on an outpatient basis 3 times a week for 8 weeks. The total dose of amphotericin B administered was 4.8 g. Thereafter, antifungal treatment was continued with itraconazole oral solution (400 mg/day) for 2 months. Follow-up chest radiograms showed complete resolution of the cavities with residual fibrous scars. The patient remained asymptomatic after an observation period of >1 year.
Discussion

*C. bertholletiae* is a rare cause of invasive mold infection [5]. Most infections have been described in patients with hematologic malignancies and neutropenia [8, 9]. Infections have also been described in transplant recipients [10, 11], a patient with AIDS [12], patients receiving deferoxamine treatment because of iron overload [13], and patients with diabetes mellitus [14]. Only 1 documented infection has been described in an immunocompetent patient [15].

Inhalation of aerosolized spores is the most probable way of acquiring *C. bertholletiae* infection, which leads to pulmonary or rhinocerebral infections. Soft-tissue infections caused by direct inoculation during trauma have been reported less frequently. Dissemination of infection occurs most often in patients with pulmonary involvement [9].

This cluster of confirmed *C. bertholletiae* infections at one hospital over 2 years is remarkable given the small number of cases so far in the literature. Some factors might have contributed to this cluster. First, high doses of chemotherapy are used with increasing frequency to treat patients with hematologic malignancies. Second, there is a growing number of solid organ transplant recipients, which increases the number of immunosuppressed patients at risk for invasive fungal infection. Third, the diagnostic workup for febrile neutropenic patients is now more invasive, with increased use of fiberoptic bronchoscopy and lung biopsy. Use of these procedures can lead to increased isolation of the responsible organisms, if specimens are analyzed by culture. Definitive identification of a hyphomycete is not possible by histological methods; culture confirmation is needed [16].

Fourth, special environmental conditions, such as construction at our hospital, might have been responsible for the cluster of infections caused by *C. bertholletiae*. Nosocomial outbreaks of airborne hyphomycosis have been reported, but these were most often caused by *Aspergillus* species [17, 18]. Construction in hospitals is a known risk factor for filamentous fungal infections of the lung because of the increased number of aerosolized spores. However, an association between pulmonary zygomycoses and construction has not been described. Fifth, the prophylactic use of itraconazole oral solution in patients with hematologic malignancies has decreased the incidence of invasive fungal infections [19, 20]. *C. bertholletiae* and several other zygomycetes are not susceptible to itraconazole. It appears that itraconazole does not provide adequate coverage for zygomycetes. The relative decrease in the incidence of other fungal pathogens during itraconazole prophylaxis might lead to the relative importance of zygomycetes as causes of opportunistic infections in immunosuppressed patients.

The clinical presentation in our cases, as in previously reported cases of *C. bertholletiae* pulmonary infections, was fever unresponsive to antibacterial chemotherapy, dyspnea, pleuritic chest pain, and infiltrates visible on chest radiograms [8, 21, 22]. Hemoptysis is a typical but infrequent manifestation of pulmonary infections caused by angioinvasive fungi such as zygomycetes or, less frequently, *Aspergillus* species. Hemoptysis was noted in 23 (26%) of 87 cases of pulmonary mucormycosis that were recently reviewed by Lee et al. [23]. It can be fatal in patients with hematologic malignancies, occurs typically after recovery of neutropenia, and can even occur in patients who are receiving appropriate antifungal treatment [24].

Pulmonary mucormycosis is often lethal, especially in patients with hematologic conditions; the mortality rate approaches 75% [23]. Antifungal treatment alone is known to be inferior to combined medical and surgical therapy for patients with pulmonary zygomycoses [25]. However, surgical intervention might not be possible in patients with hematologic malignancies because of bone marrow aplasia or multilobular lung involvement. Only 6 of the 29 previously described patients with *C. bertholletiae* infection survived [14, 21, 22, 26, 27]. Four of the 6 survivors had extrapulmonary disease. The patients who survived pulmonary infection underwent lobectomy and received antifungal therapy with amphotericin B [21].

In summary, we describe a cluster of pulmonary infections caused by *C. bertholletiae*. Three patients were receiving antifungal prophylaxis with itraconazole. Presenting symptoms were hemoptysis, fever, and dyspnea. A high index of suspicion is necessary to diagnose these infections. Therapy for underlying conditions, prompt institution of antifungal therapy, and surgical intervention when possible are necessary to improve the outcome. There is a need for new active antifungal drugs and new treatment strategies to improve the outcome of these infections.

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References