Case report

Cerebral phaeohyphomycosis in an immunodeficient child treated medically with combination antifungal therapy

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Cerebral phaeohyphomycosis is a rare fungal infection with a poor prognosis when using conventional antifungal therapy in the absence of neurosurgical intervention. We present a case of a pediatric patient with inoperable Cladophialophora bantiana cerebral abscesses. To our knowledge, this child’s case is the first reported to be treated with the combination of the newer triazole voriconazole and the new echinocandin caspofungin. Although our patient subsequently died, the natural rapid progression of the disease seemed to be altered by the antifungal combination alone, in the absence of surgery. Despite the fatal outcome for our patient, we encourage other clinicians to try unique medical approaches for this historically life-threatening infection when adjunctive surgery is impossible.

Keywords Cladophialophora, voriconazole, caspofungin, brain abscess, pediatric

Introduction

Cerebral phaeohyphomycosis is a rare infection caused by a group of dematiaceous fungi, most commonly Cladophialophora bantiana (a species previously classified as Cladosporium bantianum, C. trichoides, C. trichoides var. chlamydosporum, Xylohypha bantiana and Torula bantiana) [1]. There are at least 54 reported cases of C. bantiana cerebral infection proven by culture, but only eight of those reported are in children [2–7]. We present another case of cerebral phaeohyphomycosis caused by C. bantiana in a child. To our knowledge, this is the first reported patient treated with the combination of voriconazole and caspofungin, recently developed extended-spectrum triazole and echinocandin antifungal agents.

Case report

Our patient was an 8-year-old Asian–American male. He had a primary immunodeficiency that was of unknown origin, even though he had undergone extensive evaluations at multiple institutions. His history included recurrent Salmonella osteomyelitis, adenitis and bacteremia, Stenotrophomonas maltophilia pansinusitis, cytomegalovirus (CMV) hemophagocytic syndrome in infancy with recurrent disease later in childhood, and autoimmune hemolytic anemia. At the time of presentation to our institution he had none of these previously active infections. After a non-myeloablative conditioning regimen he underwent an unrelated cord blood transplant at our institution in April 2001. Post-transplant complications included fever, pancytopenia and recurrent CMV viremia and pneumonitis.

While febrile and neutropenic, a chest radiograph on day 8 showed nodular opacities in the right lower lobe. Subsequently, a chest computed tomography (CT) on day 9 revealed bilateral heterogeneous nodular opa-
cities, particularly in the lung bases. Though he had been on low-dose amphotericin B (0.2 mg/kg/day) for fungal prophylaxis, the medical regimen was then changed to treatment doses of amphotericin B lipid complex (ABLC) (5 mg/kg/day). Itraconazole (5 mg/kg/day) was added 13 days later, when a bronchoalveolar lavage demonstrated yeast. He was discharged from hospital on day 23 on maintenance therapy of ABLC for 1 month, while itraconazole continued for a total of 3 months. Subsequent studies showed he experienced autologous reconstitution without appreciable engraftment of donor cells. No follow-up chest radiographs or CT scans were performed during the remainder of that hospitalization or after discharge, and no central nervous system symptoms were noted.

The patient returned 3 months after transplantation complaining of a 2-week history of repetitive head and arm movements without loss of consciousness and a 1-day history of five witnessed episodes of left eye deviation. He denied any generalized seizures, fevers, trauma or illness. CT of the head with contrast revealed six enhancing mass lesions in the frontal lobe, external capsule and occipital lobe, measuring 0.6–3.5 cm in size, with surrounding vasogenic edema and mass effect compressing the lateral ventricles (Fig. 1). Neurosurgical intervention was deemed impossible due to the number and extent of lesions. A CT-guided stereotactic brain biopsy was performed and histopathological examination of haemotoxylin and eosin-stained sections revealed brown, pigmented, branched hyphae. In addition, the specimen demonstrated gliosis and a mild macrophage infiltrate with no evidence of demyelination. Culture by day 5 at 30°C yielded one colony on inhibitory mould agar with chloramphenicol and gentamicin, and no growth on brain heart infusion agar with chloramphenicol, gentamicin and cyclohex-

![Fig. 1 Brain computed tomography showing six enhancing lesions at initial diagnosis.](image-url)
imide. The mould was dematiaceous, slow growing, thermotolerant (43°C) and exhibited microscopic and colony morphology consistent with *Cladophialophora bantiana* [8]. In addition, use of an intron-specific primer [9] revealed the presence of a 558 bp intron considered to be specific for *C. bantiana sensu stricto* (Fig. 2) Antifungal susceptibility results (endpoint of MIC 80%) were 0.015 µg/ml posaconazole, 0.125 µg/ml voriconazole and 0.25 µg/ml flucytosine [10]. The fungus was preserved in a viable state in our culture collection as DUMC 112.01.

Cerebrospinal fluid exhibited normal cytological characteristics and culture was negative. Blood and urine cultures were also negative. A repeat CT of the chest revealed interval progression of the diffuse pulmonary nodules, most prominent in the left lung base; in contrast to the chest CT performed approximately 3 months earlier. A biopsy of the lung lesions was not performed as it was deemed there would be no alteration in clinical management. Antifungal therapy was changed to the combination of voriconazole (4 mg/kg/day), through compassionate release protocol, flucytosine (150 mg/kg/day) and granulocyte colony-stimulating factor-mobilized granulocyte transfusions from his father. Flucytosine levels ranged from 32 to 50 µg/ml, and a repeat head CT 1 month later revealed reduction in edema and lesion size. However, 3 months later the child developed increased lethargy and weakness on his right side. Repeat head CT at that time revealed return of edema, but cerebral lesions remained stable. The previously progressive pulmonary nodules also stabilized. Caspofungin (0.7 mg/kg/day) was then added to the voriconazole and flucytosine regimen. After 4 weeks of triple therapy, the weakness developed into hemiparesis, which then continued to total paresis (Fig. 3). Repeat CT revealed brain herniation and he died shortly thereafter. Autopsy was not granted.

**Discussion**

Cerebral phaeohyphomycosis describes infections caused by dematiaceous (melanized) fungi [2,4,7,11]. The first published case of a brain abscess caused by a fungus now identified as *C. bantiana* was in 1911 [12,13], and there are now at least 54 other reported cases of central nervous system (CNS) infections by *C. bantiana* [7]. *C. bantiana* is characterized histopathologically by darkly pigmented, sparsely branched, often moniliform, septate hyphae in unstained or hematoxylin and eosin stained tissue [2]. The characteristic brown to black, velvety colonies appear in culture within 2–14 days of incubation. The conidia of *C. bantiana* are presumed to be relatively common in nature in several known endemic areas scattered around the world, including parts of the south-eastern USA, but the species has only rarely been isolated from natural substrata [7] and never from outdoor air. Most isolations from nature have involved woody materials in rural or agricultural situations [2,7], and in many typical cases, patients may have actively disturbed the fungus’s growth habitat (e.g. by working with wood or with dusty stored plant materials) and thus become exposed to the conidia, which otherwise tend to remain attached to one another in long chains that do not readily become fragmented. Although the personal history of the current patient is not completely known, he is known to have come originally from China, where
C. bantiana infection has not been reported [7], and to have lived in several urban settings in the USA as his parents sought treatment for his condition. Thus his case suggests that urban-dwelling immunocompromised individuals may be at risk of infection within endemic zones for this species.

At least 16 reported C. bantiana cases have involved dogs or cats [2,7]. The entry portal in human cases is not clear, although it has been speculated that it might be the lung, skin or ear, from which hematogenous spread to the CNS occurs [15]. Unfortunately, C. bantiana rarely has been isolated from these sites in patients.

Phaeohyphomycosis of the central nervous system due to C. bantiana generally occurs in males of an average age of 37 years, and although cases occur worldwide, most isolates have been reported from the USA [7]. There appears to be no racial predilection. The previously reported cases reveal a mixture of both immunocompromised as well as immunocompetent patients (33 and 20 patients, respectively). In only nine patients, however, has the degree of immunological compromise been specifically outlined in detail [7]. The CNS manifestations of C. bantiana are brain abscesses and chronic meningoencephalitis [3,16]; the most common presenting symptoms are headaches, focal neurological deficits, hemiparesis, cranial nerve deficits, or seizures. These symptoms often are due to mass effect and can last from weeks to as long as 5 years [2].

In our review of all published English-language pediatric cases (Table 1), five of the six cases of C. bantiana cerebral infection presented with brain abscesses, while one had chronic meningoencephalitis. Four were confirmed by culture [4,16,17,19]; the other two were identified by methenamine silver stain and direct inoculation into mice with subsequent identifica-
Two patients were thought to have relative immunosuppression, as one had already endured a previous fungal infection and the other had been on corticosteroids [15,17]. All of the patients with abscesses had the lesion partially or completely drained or removed surgically. However, even with adjunctive surgical management, only two of five survived at least 10 months after follow-up [4,15–18], with one patient lost to follow-up [19]. Only three received systemic antifungal treatment, consisting of either fluconazole or amphotericin B monotherapy, or the combination of amphotericin B plus flucytosine [3,4,17].

The poor prognosis for cerebral infections caused by filamentous fungi, including *C. bantiana*, is generally thought to be due to the inability to make the diagnosis, incomplete abscess encapsulation, presence of multiple lesions, resistance to antifungal therapy, or complications of surgical or medical therapy [3,4]. The various treatments for *C. bantiana* have included surgical resection as well as antifungal therapy. Unfortunately, medical treatment has historically been unsuccessful and surgical excision offers the best prognosis. Prior to 1989, amphotericin B and flucytosine were the only antifungals with activity against *C. bantiana*. According to one review, during that time no patient survived who did not undergo surgical resection. Of those who underwent resection, only nine survived follow-up; however, no specific follow-up duration was reported [2]. In more recent years, fluconazole and itraconazole have been utilized; however, the results have been just as poor [3,7]. In the largest review of 54 cases of cerebral disease, the duration of disease is reported in 22 cases: it averages 6 months after the first symptoms were noted. However, no information was given in that review to distinguish cases in which adjunctive surgery was undertaken [7].

Voriconazole (Vfend®; Pfizer Pharmaceuticals, New York, NY, USA) is a new second-generation triazole [20,28–31] that has demonstrated efficacy *in vitro* equal to or greater than that of amphotericin B and itraconazole against moulds in genera such as *Alternaria*, *Cladosporium*, *Acremonium*, *Chrysosporium*, and *Fusarium* [21–23]. Previous *in vitro* studies with *C. bantiana* have shown low minimum inhibitory concentrations (MIC) for voriconazole, itraconazole, amphotericin B [24], and terbinafine [24–26]. While amphotericin B and flucytosine have been considered the standard antifungal agents due to lack of better alternatives, voriconazole may be a new clinically appropriate agent to use against *Cladophialophora* species and other CNS mould infections due to its improved brain tissue penetration [27].

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Presentations</th>
<th>Antifungal treatment</th>
<th>Surgical treatment</th>
<th>Outcome</th>
<th>Year/Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Abscess</td>
<td>None</td>
<td>Aspiration</td>
<td>Lost to follow-up</td>
<td>1962/17</td>
</tr>
<tr>
<td>2</td>
<td>Chronic meningitis</td>
<td>None</td>
<td>Aspiration</td>
<td>Dead after craniotomy</td>
<td>1971/14</td>
</tr>
<tr>
<td>3</td>
<td>Abscess</td>
<td>Amphotericin B</td>
<td>Partial excision</td>
<td>Died 8 days after surgery</td>
<td>1974/15</td>
</tr>
<tr>
<td>4</td>
<td>Abscess</td>
<td>Flucytosine</td>
<td>Gross total resection</td>
<td>Died 8 months after surgery</td>
<td>1979/16</td>
</tr>
<tr>
<td>5</td>
<td>Abscess</td>
<td>Amphotericin B, Flucytosine</td>
<td>Partial excision</td>
<td>Survived at least 10 months</td>
<td>1981/13</td>
</tr>
<tr>
<td>6</td>
<td>Abscess</td>
<td>Fluconazole</td>
<td>Aspiration</td>
<td>Died 8 months after surgery</td>
<td>1993/4</td>
</tr>
</tbody>
</table>

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(Cancidas®; Merck, Rathway, NJ, USA) is a new echinocandin class antifungal that interferes with cell wall biosynthesis by non-competitive inhibition of 1,3β-D-glucan synthase [32]. Only one study has examined activity of caspofungin against C. bantiana and it displayed in vitro potency inferior to that of the triazole posaconazole [33].

Despite conventional therapy, the prognosis of patients with cerebral C. bantiana is very poor. Our patient developed clinical symptoms while receiving therapeutic doses of both a lipid product of amphotericin B and itraconazole. Initially, the patient showed clinical and radiographic improvement for 2 months with the combination of voriconazole and flucytosine. However, with the lack of immune reconstitution in the patient, neither the combined voriconazole plus flucytosine that had shown potent in vitro activity against the mould nor the voriconazole plus flucytosine plus caspofungin combination could stop the eventual progression of disease. The continued progression of infection in this case emphasizes the essential importance of an effective host immune response as well as the role for neurosurgical intervention in bringing about a positive outcome in C. bantiana cases, a generality supported by reviews showing that no patient with a cerebral infection caused by this fungus has survived without surgical excision of the lesion [2,7].

There has been a recent explosion of newer antifungals in development, offering new therapeutic choices for invasive mycoses. The standards of antifungal care are shifting to include these newer agents for historically recalcitrant fungal infections. However, the importance of an effective host immune system will remain paramount for a good outcome. It is crucial that these newer antifungals are creatively utilized for treatment of these less common and deadly moulds and that more clinicians report both their positive and negative experiences. Our patient was unable to undergo surgery and the antifungal combination we used appeared to reduce the edema and size of lesions. However, we believe that his lack of a functioning immune system was also a critical factor in his fatal outcome.

References


