

Successful Treatment of Cerebral Pheohyphomycosis Caused by *Cladophialophora bantiana* Infection in a Solid Organ Transplant Patient: A Case Report and a Review of Literature

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Abstract

We present a case of a 60-year-old male with a past medical history of alpha-1-antitrypsin deficiency with lung transplantation in 2010, who was maintained on immunosuppressive agents, and was admitted to the hospital for neurological symptoms. Magnetic resonance imaging (MRI) of the brain revealed a ring-enhancing lesion. Microscopic evaluation of the abscess revealed fungus, and cultures grew *Cladophialophora bantiana* (*C. bantiana*). He was successfully treated with surgical abscess excision, liposomal amphotericin B and voriconazole.

Keywords: *Cladophialophora bantiana*; Solid organ transplant; Antifungals

Introduction

Cerebral pheohyphomycosis is a rare and frequently fatal fungal infection of the brain typically caused by *Cladophialophora bantiana* (*C. bantiana*), *Exophiala dermatitidis*, and *Rhinocladiella mackenziei*, all of which belong to the order *Chaetothy-*

iales [1]. These fungi are known as phaeoid or dematiaceous fungi, and are routinely characterized by intense melanin-like pigmentation of their cell walls, which is readily observed in hematoxylin and eosin stained sections [2]. Its mortality rate is high despite aggressive treatment [3]. *C. bantiana* accounts for the majority of cerebral pheohyphomycosis documented to date, and they are known to be highly neurotropic [3]. We report a case of cerebral pheohyphomycosis caused by *C. bantiana* successfully treated with surgical excision of the abscess, liposomal amphotericin B, and voriconazole.

Case Report

On September 30, 2014, a 60-year-old male with a past medical history of alpha-1-antitrypsin deficiency diagnosed in 1989, who was status post lung transplantation in 2010, was admitted to the hospital for increased headache, photophobia, and gait disturbances. He had been in his baseline state of compromised health until about 7 days prior to this admission. He began noticing headaches that were located in the back of his neck, and were unremitting in nature. Then, 1 - 2 days prior to the admission, he started to have gait abnormalities. The patient denied having these symptoms before.

He had been on immunosuppressant agents including oral tacrolimus 1 mg twice daily, oral azathioprine 200 mg daily, and oral prednisone 5 mg daily. In addition, he had been on antibiotic prophylaxis including oral azithromycin 250 mg every Monday, Wednesday, and Friday, and oral trimethoprim/sulfamethoxazole (TMP/SMX) 800 mg/160 mg every Monday, Wednesday, and Friday.

His vital signs included a temperature of 97.9 °F (36.6 °C), heart rate of 74/min, respiratory rate of 18/min, blood pressure of 132/82 mm Hg, and an oxygen saturation of 96% on room air. The physical examination was unremarkable. He was alert, awake, and conversant with clear speech and mental status. His cranial nerves were well preserved with no nystagmus. Dysmetria and dysidiadochokinesia were present, and were more obvious on the right side of the body. He moved all four extremities reasonably with adequate muscle bulk and tone. There was no frank pronator drift or leg lag.

Laboratory findings included a white blood cell (WBC)

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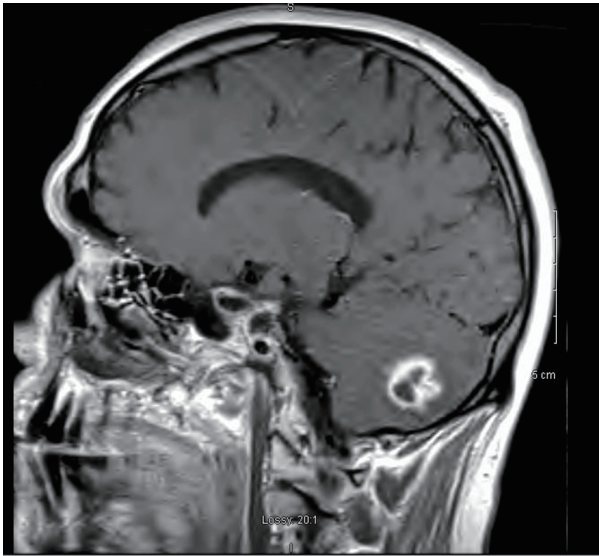


Figure 1. Magnetic resonance imaging (MRI), sagittal view. There is a 2.0 cm lobulated ring-enhancing right cerebellar mass with central restricted diffusion consistent with abscess. There is significant edema, mass effect and compression of the fourth ventricle.

count of 2.6/mm³, platelet count of 99,000/μL, and hemoglobin of 11.7 g/dL. The chemistry panel revealed sodium of 137 mg/dL, potassium of 4.3 mg/dL, calcium of 9.2 mg/dL, creatinine of 1.2 mg/dL, blood urea nitrogen (BUN) of 26 mg/dL and chloride of 101 mg/dL.

A magnetic resonance imaging (MRI) of the brain (Fig. 1) revealed a 2.0 cm lobulated rim-enhancing right cerebellar mass with central restricted diffusion consistent with abscess.

Aspiration of the abscess revealed *Staphylococcus sciuri*. A peripherally inserted central catheter was placed and he was

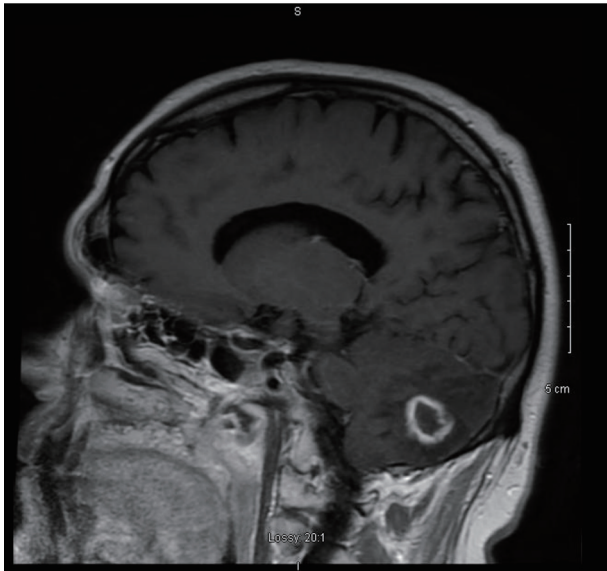


Figure 2. MRI, sagittal view. There is a 1.6 × 1.8 cm ring-enhancing right cerebellar mass with extensive surrounding vasogenic edema and compression of the fourth ventricle.

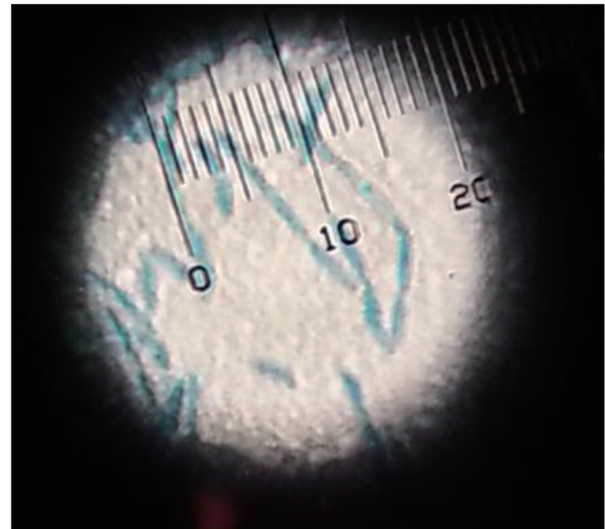


Figure 3. Lactophenol cotton blue preparation demonstrated pigmented septate hyphae.

discharged home on intravenous (IV) meropenem and vancomycin for a duration of 6 weeks.

On December 10, 2014, the patient was admitted once more for worsening headaches and photophobia. The headaches started 5 days before his admission, and were located behind his right eye. He was very unstable on his feet, and the left side of his body displayed weakness. He denied any nausea, vomiting, blurred vision, fever, chills or sweats. His vital signs were within normal limits and the physical examination was unremarkable.

Laboratory findings included a WBC count of 7.5/mm³, platelet count of 95,000/μL, and hemoglobin of 11.2 g/dL.

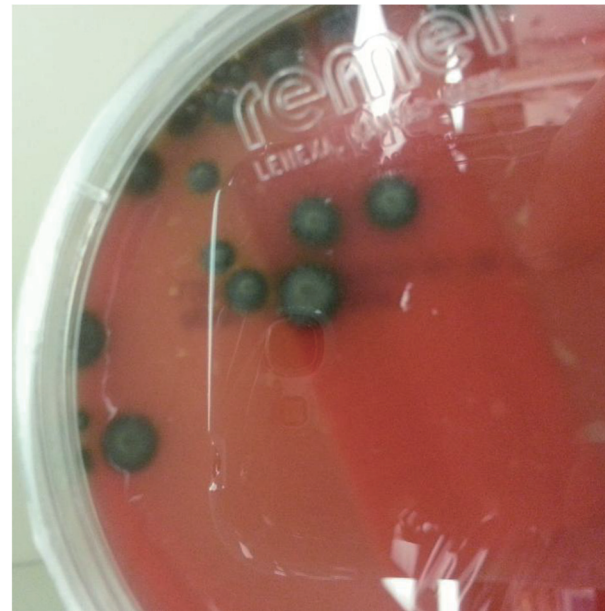


Figure 4. Sheep red blood agar plate grew mucoid dark pigmented colonies.

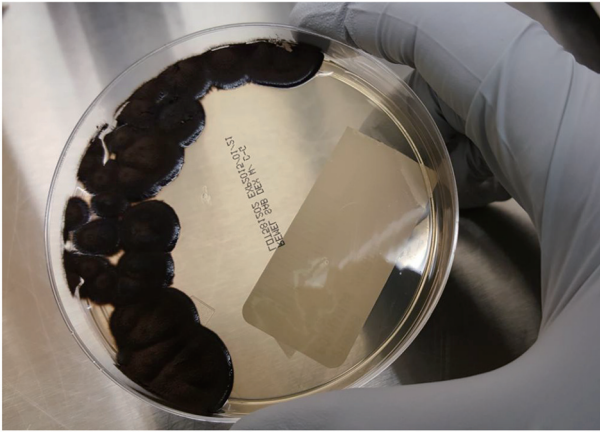


Figure 5. Sabouraud agar plate grew mucoid dark pigmented colonies.

Electrolytes demonstrated sodium of 135 mg/dL, potassium of 4.1 mg/dL, chlorine of 103 mg/dL, BUN of 20 mg/dL and creatinine of 1.1 mg/dL.

A repeat MRI of the brain (Fig. 2) revealed a right 1.6 × 1.8 cm rim-enhancing right cerebellar mass with extensive surrounding vasogenic edema. The patient underwent a stealth directed resection of the right cerebellar brain abscess. Samples from this procedure ultimately grew fungus (Figs. 3-5). The patient was empirically treated with course of IV liposomal amphotericin B for a duration of 6 weeks and voriconazole for a duration of 12 weeks. The patient was treated successfully and his neurologic deficits improved.

Discussion

Cerebral pheohyphomycosis is a rare infection caused by the fungus *C. bantiana*. *C. bantiana* is a member of the order *Chaetothyriales*, which is often referred to as “black yeast-like fungi” due to the ability of some representatives to produce budding cells as well as dark hyphae, depending on the life cycle and environmental conditions [4]. It is the most common cause of central nervous system (CNS) infections caused by the dematiaceous pigmented fungi [5]. The pigmented nature of this organism has been shown to be due to melanin production, and this feature may assist the organism with evading host defenses [6, 7].

Although the portal of entry for infection is frequently obscure, many fungi are thought to be blood-borne from the lungs or intestines [7, 8]. Primary infection in the middle ear and paranasal sinuses can subsequently spread to the CNS [8]. It can present in the form of cerebritis, meningitis, or abscess (most common clinical manifestation) [5, 9-11].

The risk factors for *C. bantiana* infection include those which suppress cell-mediated immunity, such as organ transplantation, cancer, and immunosuppressive agents [12]. In one study by Chakrabarti et al, researchers revealed that the majority of these cases were found in males who came from Asian countries [13]. Interestingly, *C. bantiana* infection was nearly equally distributed in the immunocompetent and the immunosuppressed hosts [13]. The most common symptom

was headaches, followed by hemiparesis, seizures, and altered sensorium [13, 14].

Histopathological and microbiological examinations are the diagnostic tool of choice since fungal brain abscess cannot be differentiated from bacterial cerebral abscess, primary CNS tumor, and cerebral metastasis by imaging studies, according to Huang et al [15]. However, a study done by Hauck et al mentioned that magnetic resonance diffusion-weighted imaging apparent diffusion coefficient MRI may add valuable information for the imaging differential diagnosis of fungal abscess versus bacterial abscess versus high-grade glioma [16]. There has also been use of genetic analysis to help in the diagnosis of *C. bantiana* in China [15].

Current treatment recommendations in solid organ transplant (SOT) patients from the American Society of Transplantation Infectious Diseases Community of Practice regarding pheohyphomycosis identify itraconazole, voriconazole, and posaconazole as first-line therapy [17-19]. Amphotericin B is not recommended as a first-line therapy in the setting of cerebral abscess due to concern for excess failure rates [19]. However, our study noted voriconazole and amphotericin B were the most commonly used antifungal agents. Voriconazole has been used in a number of case reports due to its broad activity against dematiaceous fungi and its good cerebrospinal fluid penetration. The use of itraconazole has excellent brain tissue penetration and can be used if voriconazole cannot be tolerated [20]. Flucytosine is effective; however, its use is limited due to bone marrow suppression, especially in immunocompromised patients [21]. Fluconazole and echinocandins are not effective against *C. bantiana* [21].

The *Staphylococcus sciuri* was ultimately believed to be a skin contaminant. This delayed appropriate antifungal therapy and underscores the need for surgical resection of the abscess for diagnosis and treatment.

We reviewed the literature (Table 1 [21-29]) of patients who underwent SOT that were subsequently on immunosuppressant therapy and developed this rare CNS infection. The average age was 39 years and the median age was 38 years. There were six males and four females. Five patients had kidney transplant, two patients had liver transplant, three patients had heart transplant, and two patients had lung transplant. The most common types of immunosuppressive agents used were corticosteroids, azathioprine, and cyclosporine. The most common presentation was headache. Thirty percent of the patients had an abscess located in the parietal region and cerebellum, 20% in the temporoparietal region, and 10% in the frontal region. The most common antifungal agent used was amphotericin B. Six patients expired and three patients were cured.

Conclusion

Cerebral pheohyphomycosis is a deadly infection with high morbidity and mortality, despite aggressive treatment. Complete excision of brain lesions may provide better results than simple aspiration. An aggressive medical and surgical approach is warranted in treating these infections to optimize outcomes. Although rare, it is important for clinicians to keep this fungal infection in their differential diagnosis.

Table 1. Review of Literature of *Cladophialophora* Infection in Solid Organ Transplant Patients [21-29]

| Reference | Age | Gender | Organ transplanted | Immunosuppressant | Presentation | Location | <i>Cladophialophora</i> | Management | Outcome |
|-----------|-----|--------|--------------------|--|---|---|-------------------------------------|---|---|
| [21] | 50 | M | Liver | - | Confusion, left hemiparesis, lethargy and slurred speech progressing to coma | Right temporoparietal | <i>C. trichoides</i> | Inoperable | Expired 7 days after diagnosis |
| [22] | 25 | F | Kidney | Prednisolone, azathioprine, cyclosporine | Generalized seizures, right hemiparesis | Left parietal | Unspecified pheohyphomycosis | CT-guided stereotactic aspiration, amphotericin | Expired 1 month after aspiration from fulminant hepatitis from hepatitis C and B, and a CMV infection leading to sepsis |
| [22] | 51 | M | Kidney | Prednisolone, azathioprine | One episode of generalized seizure, headache and vomiting for 10 days | Left parietal | Unspecified pheohyphomycosis | CT-guided stereotactic aspiration, liposomal amphotericin, craniotomy with abscess excision | Cured |
| [23] | 6 | M | Liver | - | Right-sided focal seizures | Left frontal lobe | <i>C. bantiana</i> | Aspiration, amphotericin, craniotomy with abscess excision | Cured |
| [24] | 35 | M | Kidney | Prednisolone, cyclosporine, azathioprine | Two episodes of generalized tonic clonic seizures over 4 months, headache and vomiting for 1 month | Right parietal | <i>C. trichoides</i> | Excision, amphotericin B | Cured |
| [25] | 57 | - | Heart | Prednisolone, azathioprine, FK 506, anti-T lymphocyte globulin | Nausea and ataxia | Right cerebellar | <i>C. bantiana</i> | Stereotactic aspiration, surgical excision, initially amphotericin B and 5-fluorocytosin, was switched to itraconazole | Abscess recurrence with spread and fatal septic shock |
| [26] | 41 | F | Heart, lung | Mycophenolate mofetil, tacrolimus, prednisone | Right facial numbness, right upper molar tooth pain, right earache, diplopia, and right frontotemporal headache | Right cerebellar | <i>C. bantiana</i> | Craniotomy with abscess excision, liposomal amphotericin B, voriconazole, recurrence with repeat craniotomy | Expired 45 days after presentation |
| [27] | 30 | F | Heart | Methotrexate, tacrolimus, mycophenolate mofetil | Presented 5 weeks after beginning treatment for lung infection with headaches | Left cingulate gyrus | Unspecified <i>Cladophialophora</i> | Fungal pneumonia was tx with amphotericin B lipid complex, but was switched to liposomal amphotericin B after brain abscess diagnosed, excisional biopsy, then switched to itraconazole | Expired about 4 months after cerebral abscess identified |
| [28] | 36 | F | Kidney | Cyclosporine, azathioprine, prednisolone | Frontal headaches and left arm weakness | Three separate lesions in unspecified locations within white matter | <i>C. bantiana</i> | Stereotactic guided biopsy, liposomal amphotericin B, fluconazole with itraconazole and discontinuation of azathioprine | Was still being treated 12 months out with itraconazole and fluconazole, CT scan showed regression with mild inflammation remaining |
| [29] | 61 | M | Kidney | Cyclosporine, azathioprine, prednisone | Right hemiparesis | Left parietotemporal | <i>C. bantiana</i> | Craniotomy with abscess excision, fluconazole, dexamethasone, recurrence treated with another craniotomy/excision, amphotericin B and fluconazole | Developed septic shock from <i>E. coli</i> and expired 1 month and 12 days after initial diagnosis |
| Our case | 60 | M | Lung | Cyclosporine, azathioprine, prednisone | Gait instability, headaches, photophobia | Right cerebellar | <i>C. bantiana</i> | Stealth directed resection/ liposomal amphotericin B voriconazole | Cured |

C. bantiana: *Cladophialophora bantiana*; *C. trichoides*: *Cladophialophora trichoides*; CT: computed tomography; CMV: cytomegalovirus; *E. coli*: *Escherichia coli*.

Conflict of Interest

The authors have no conflict of interest to disclose.

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