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Case Report

Intracranial fungal *Cladophialophora bantiana* infection in a nonimmunocompromised patient: A case report and review of the literature

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ABSTRACT

Background: *Cladophialophora bantiana* is a dematiaceous fungus that rarely infects the central nervous system (CNS). It is associated with a mortality rate of over 70% despite treatment.

Case Description: An 81-year-old female with a remote history of renal cell carcinoma presented with progressive headache and an expressive aphasia for 3 days. Computed tomography imaging revealed a left frontotemporal mass with surrounding vasogenic edema. A left frontotemporal craniotomy was performed and cultures revealed *C. bantiana*. The initial management with IV voriconazole was unsuccessful and the patient had a recurrence of the cranial infection and developed pulmonary abscesses. Following the addition of oral flucytosine, the patient showed a significant improvement with a complete radiographic resolution of both the cranial and pulmonary lesions.

Conclusion: *C. bantiana* involving the CNS is a rare and often fatal disease. Surgical management along with standard antifungal treatment may not provide definitive therapy. The addition of flucytosine to IV voriconazole resulted in a positive outcome for this patient who is alive, living independently 1 year from the original diagnosis. In this rare fungal infection, standard antifungal treatment may not provide adequate coverage and the utilization of additional therapy may be required.

Keywords: Central nervous system, *Cladophialophora bantiana*, Cranial abscess, Flucytosine, Fungal, Infection

INTRODUCTION

Dematiaceous fungi are identified by the melanin-containing hyphae and conidia that provide the darkly pigmented color for which they are named.[5] One such species that causes phaeohyphomycosis in humans is *Cladophialophora bantiana* which is found mainly in soil and decaying vegetation throughout the world. The fungus infects both the immunocompetent and immunocompromised and typically causes mild sinusitis or allergic rhinitis. Phaeohyphomycosis of the central nervous system (CNS) is rare but typically presents as a cerebral abscess.[2] Treatment entails surgery and systemic antifungal medications. Despite aggressive treatment, the mortality rate is over 70%[3] and if untreated may be as high as 100%.[8]

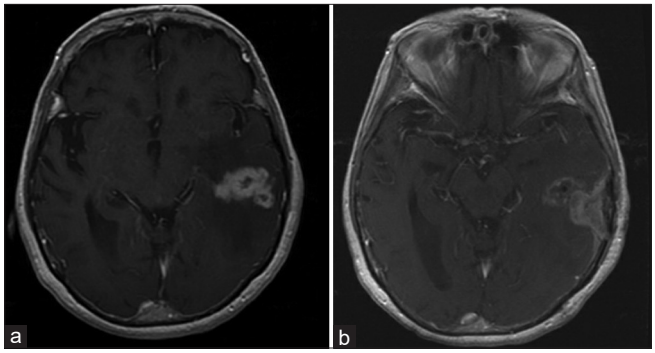

Figure 1: (a) Initial contrast-enhanced T1-weighted axial MRI scan demonstrating a heterogeneously enhancing mass in the left temporal lobe with surrounding vasogenic edema. (b) Immediate postoperative contrast enhanced T1-weighted axial MRI.

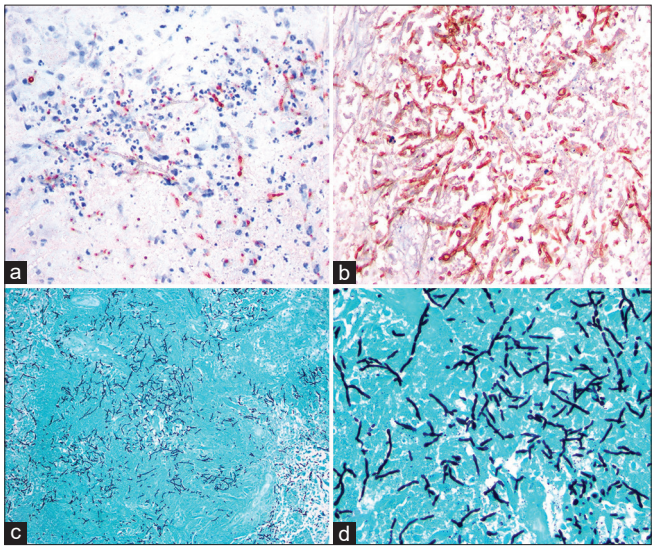

Figure 2: *Candida* immunohistochemical test low power (a), (b) *Candida* IHC test high power, (c) Grocott's methenamine silver stain showing budding hyphae low power, and (d) GMS high power.

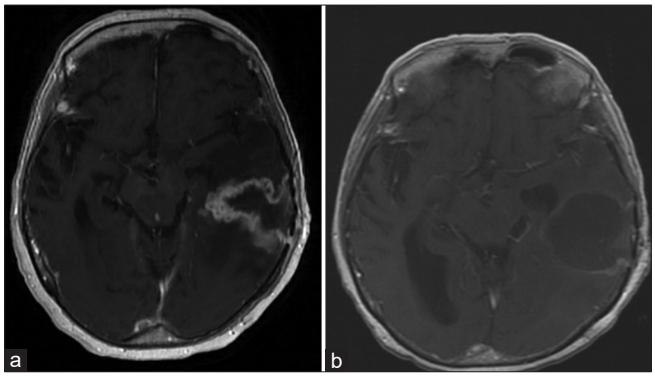

Figure 3: (a) Six-week follow-up contrast-enhanced axial T1-weighted MRI showing disease progression with worsening edema and mass effect. (b) One-week postoperative redo craniotomy T1-weighted contrast-enhanced T1 axial MRI showing worsening edema with a new cystic collection with mass effect and developing communicating hydrocephalus.

Various medications have been used for the treatment of CNS *C. bantiana* including the broad-spectrum antifungal amphotericin B. Treatment failure and risks of serious side effects have changed the treatment paradigm to the use of newer azole drugs which offer important advantages including the availability for oral treatment and low risk for nephrotoxicity. Infections of the CNS pose multiple challenges including determining the duration of treatment and the need for permeating the blood–brain barrier. In resistant cases, the need for combination treatment may be necessary. The antimetabolite drug flucytosine, once used as a stand-alone therapy for systemic fungal infections, has been used with amphotericin B in reported cases, although the outcomes have been mixed. Here, we report the successful use of concomitant treatment with flucytosine and voriconazole in a patient with disseminated black mold infection.

CASE PRESENTATION

An 81-year-old Caucasian female with a remote history of renal cell carcinoma, hypertension, and pulmonary nodules presented to the hospital with 3 days of headaches and confusion. On examination, the patient was found to have an expressive aphasia. Computed tomography (CT) of the head demonstrated a heterogeneously enhancing left temporal mass with surrounding edema concerning for a primary neoplasm. The patient was then transferred to our institution for neurosurgical consultation. Brain magnetic resonance imaging (MRI) with contrast was completed revealing a heterogeneously enhancing mass involving the left temporal lobe with extensive vasogenic edema raising concern for glial neoplasm [Figures 1a and 1b]. The patient was administered intravenous dexamethasone without any improvement. Ultimately, a left frontotemporal craniotomy was performed with intraoperative findings consistent with abscess formation. The final pathology report described necrotizing granulomatous inflammation and immunostaining that was positive for *Candida* but negative for neoplasia. Cultures obtained intraoperatively grew *C. bantiana* [Figures 2a-d]. The patient recovered well postoperatively and was discharged home on intravenous (IV) voriconazole.

Six weeks following initial operative management, the patient was readmitted with worsening confusion and repeat imaging demonstrated a recurrent abscess with significant edema and midline shift [Figures 3a and b]. Understanding the risks for permanent neurologic deficit, the patient's husband agreed to a "re-do" craniotomy and a gross total resection was achieved. The operative cultures remained negative, however, pathologic review again demonstrated *Candida* colonization. The patient developed communicating hydrocephalus and required an external ventricular drain. The CSF culture samples drawn during ventricular drainage were consistently

Table 1: Summary of data on cases of *Cladophialophora bantiana* regarding various flucytosine and azole treatments.

Reference	Patient age/sex	Abscess region	Treatment (if any)	Mortality
3	20 Y, M	Right frontal lobe	Amphotericin (IV), flucytosine, oral itraconazole	Yes
4	79 Y, F	Right frontal region	Amphotericin B, flucytosine, voriconazole	Yes
Presented case	81 Y, F	Left frontal-temporal region	IV voriconazole, oral flucytosine	No

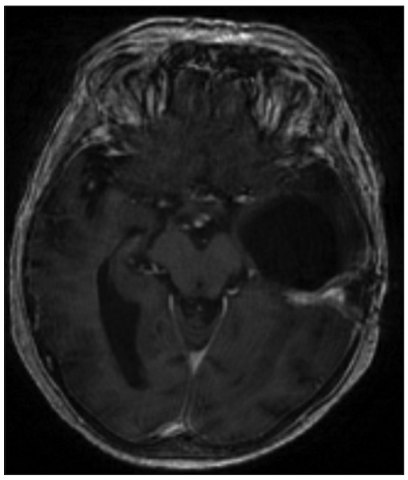

Figure 4: Eight-month follow-up contrast-enhanced T1 axial MRI showing ex vacuo changes with resolution of the disease.

negative for both fungus and bacteria, and the intracranial pressure remained low. CT imaging of the sphenoid and maxillary sinuses demonstrated pansinusitis. A chest X-ray performed during the patient's ICU stay revealed the right upper lobe lesion, confirmed by CT as a cavitary lesion of the right upper lobe with hilar lymphadenopathy. A PET scan was completed revealing multiple lesions in the right lung making the patient a poor candidate for thoracic surgery intervention. Palliative care was consulted and the family did not want to pursue any further aggressive care. Oral flucytosine was added to the IV voriconazole, and the patient and family ultimately opted to transfer home with assistive services.

Remarkably, the patient had a significant improvement at her 6-week follow-up visit and an MRI of the brain showed decreasing size of the temporal lesion. A 8-month follow-up showed complete resolution of the left temporal lesion [Figure 4]. The patient is home doing well carrying out many of her activities of daily living.

DISCUSSION

C. bantiana carries a high mortality when involving the CNS despite aggressive surgical and pharmacologic treatment.[10] In this case report, we describe the successful treatment of an immunocompetent patient with disseminated phaeohyphomycosis using flucytosine in addition to the typical therapy of cranial surgery and voriconazole. One year from presentation, the patient is living at home with some speech difficulties but no imaging findings to suggest recurrent disease.

Four organisms are primarily responsible for cerebral phaeohyphomycosis: *Cladosporium trichoides, Xylohypha bantiana, Cladosporium bantianum*, and *C. bantiana*. These four organisms fall under the mycological category of *C. bantiana*.[7] The diagnosis of phaeohyphomycosis is dependent on pigmented fungal organisms in histopathology. Dematiaceous fungi like *C. bantiana* are more commonly found in tropical and subtropical areas of the world such as Saudi Arabia, India, or Pakistan.[1,6,7,11]

CNS invasive *C. bantiana* is relatively uncommon and carries a nearly 70% mortality rate despite surgery resection and use of systemic antifungal treatments.[8] Typical presenting symptoms include headache, nausea, and confusion. In a review of 101 cases of CNS phaeohyphomycosis, more than half of the patients had no identified immunocompromising risk factors and underwent aggressive surgical management in combination with antifungal treatment. There is no consensus treatment approach and the duration of antifungal therapy is mostly based on case reports and murine studies.[9] Overall, treatment failure in immunocompetent patients due to recurrent intracerebral abscesses and systemic disease remains high.[3]

Amphotericin B has long been considered the mainstay of treatment and more recently, in combination with flucytosine.[3,8] Few case reports in the literature describe the use of voriconazole and flucytosine.[4] Our case is unique in that we offer long-term follow-up affirming clinical and radiographic resolution of the patient's cerebral and pulmonary lesions.

Flucytosine is a pro-drug of 5-fluorouracil (5-FU) that acts as a purine and pyrimidine uptake inhibitor and is used as a fungistatic agent in conjunction with an antifungal such as amphotericin B for the treatment of cryptococcal pneumonia or *Candida* sepsis in immunocompromised patients. Within the fungal organism, flucytosine metabolizes to flucytosine 5-FU which inhibits both DNA and RNA synthesis. The medication has been around for more than a half of a century; however, increased resistance and the risk of nephrotoxicity and bone marrow suppression have shifted therapy toward newer medications.

Our patient's initial treatment consisted of a complete surgical resection of the mass followed by systemic

amphotericin B. When the patient returned with a recurrence of the abscess, the treatment was shifted to IV voriconazole. While amphotericin B remains the gold standard for the treatment of invasive fungal infections, its efficacy is limited, with response rates ranging widely from 10% to 80%.[11] In our presented case, the single agent antifungal voriconazole was used with limited effectiveness. The patient developed a communicating hydrocephalus; however, the decision was made to forgo intrathecal treatment and a palliative approach was implemented. With the addition of oral flucytosine to IV voriconazole, the patient had a remarkable recovery. 5-FU is an antimetabolite and plays an important role in a new therapeutic approach in the treatment of certain tumors, especially colorectal carcinoma.[12] Murine models have demonstrated flucytosine efficacy when used in combination with posaconazole or the triple combination of micafungin, posaconazole, and flucytosine.

Historically, systemic treatment for *C. bantiana* has included amphotericin B and more recently – azoles such as voriconazole, itraconazole, ketoconazole, and fluconazole see [Table 1]. These medications work by blocking the fungal cytochrome p450 enzyme thus inhibiting the synthesis of ergosterol which is essential to the fungus cell membrane. Flucytosine, historically, has been used in combination with amphotericin B, however, has been replaced with the newer azole drugs.

As cases of phaeohyphomycosis continue to rise the need for more efficacious therapies must be identified as treatment options. Stand-alone treatment with a single agent antifungal regimen may not be sufficient. This rare case highlights the use of a multifaceted approach, including the use of older generation medications with good outcome.

CONCLUSION

We present a rare case of a fungal brain abscess caused by *C. bantiana* (black mold). Our patient's lesion initially originated in the left frontal-temporal region and rapidly disseminated throughout the entire right lung, including a lesion to the right upper lung. Complete surgical resection followed by combination antifungal medications resulted in clinical and radiographic resolution at 1-year follow-up.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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