

CASE REPORT

A CLADOPHIALOPHORA BRAIN ABSCESS IN A RENAL TRANSPLANT RECIPIENT

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Abstract. *Cladophialophora bantiana* is a dematiaceous fungus with neurotrophic propensity for which therapy is not standardized and mortality is high. We report here a 49 year old non-diabetic renal transplant patient on triple immunosuppressant therapy who presented with a history of falls, weakness and headaches. A computed tomography scan of the brain revealed a 30 mm diameter abscess in the brain which was removed surgically and diagnosed on culture as *C. bantiana*. The patient was successfully treated medically post-operatively with chronic posaconazole. We review the literature regarding central nervous system infections due to *C. bantiana*.

Keywords: *Cladophialophora bantiana*, brain abscess, posaconazole, renal transplant

INTRODUCTION

The incidence and prevalence of human mycotic infections is currently on the rise (Pfaller *et al*, 2006). One group of opportunistic fungal pathogens is characterized by a dark pigment (Revankar and Sutton, 2010). These fungi are broadly classified as phaeohyphomycosis (Revankar and Sutton, 2010). Most fungi that cause cerebral phaeohyphomycosis produce mainly brain abscess as opposed to disseminated infection (Revankar *et al*, 2004). The neurotropic *Cladophialophora bantiana* is an important etiological agent in this group and is associated with a very grave prognosis (Revankar *et al*, 2004).

C. bantiana infection has been reported from different parts of the globe unlike *Rhinocladiella mackenziei* (formerly *Ramichloridium mackenziei*), another highly fatal agent of cerebral phaeohyphomycosis, which is confined primarily to middle-eastern countries (Taj-Aldeen *et al*, 2010). We report here a case of multiloculated brain abscess caused by *C. bantiana* in a renal transplant recipient and explore the therapeutic approach for this life threatening infection.

CASE REPORT

A 49 year old non-diabetic female patient from Myanmar who had previously undergone renal transplantation presented to Apollo Gleneagles Hospitals in Kolkata, India with headache, weakness and occasional falls in November 2013. The patient had a history of end stage renal disease due to cresenteric glomerulo-

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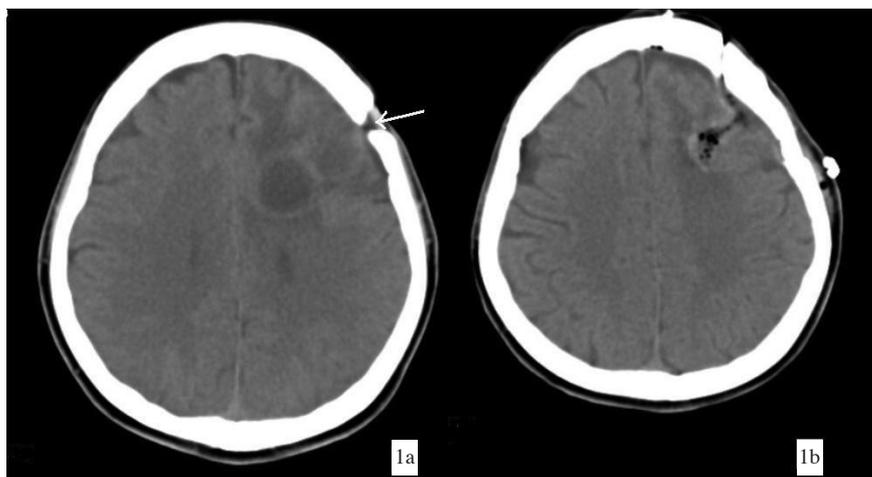


Fig 1(a)–Preoperative CT scan of brain showing hypodense SOL (30 x 30 mm) in the left frontal lobe. The white arrow indicates burr hole from previous surgery. 1(b) Post Preoperative CT scan of brain showing absence of the frontal SOL.

nephritis for which renal transplantation was performed 3 years previously. The patient was on triple immunosuppressant therapy with tacrolimus (1 mg BD), mycophenolate mofetil (250 mg OD) and prednisolone (10 mg OD). The patient stated she had similar symptoms four months previously for which she underwent cranial burr-hole surgery in Myanmar in August 2013. No documents were available from Myanmar. She was not taking any antibiotics or antifungal medications at the time of presentation. There was no history of vomiting, convulsions or fever.

On physical examination her pulse and blood pressure were within normal limits. Neurological examination revealed no sensory or motor neurone deficits. Although there was no focal neurological deficit, but the patient had problems in sustained attention and was also found to have executive dysfunction and gait apraxia. The patient had a healed scar over the left frontal area of her scalp.

A computed tomography (CT) scan of

the brain was conducted, which showed a 30 x 30 mm hypodense mass with a smooth thin wall with peri-mass edema in the left frontal cerebrum consistent with an abscess (Fig 1a). The neurosurgeon performed a left frontal craniotomy and the mass was removed en total (Fig 1b).

On pathological examination, the mass appeared grayish white, encapsulated and nodular (Fig 2a). At transection of the mass revealed a cystic cavity filled with pus. Microscopic examination of the capsular pus after digestion with KOH revealed numerous brown pigmented branching hyphae along with brown pigmented septate round bodies (Fig 2b). A Grocott's methanamine silver stain revealed chained, elongated fungal elements. Histology of the abscess cavity showed a wall composed of fibrocollagenous tissue lined by granulation tissue with mixed acute and chronic inflammatory cells, histiocyte aggregates, foreign body type and Langhans' giant cells along with several acute angle septate fungal hyphae.

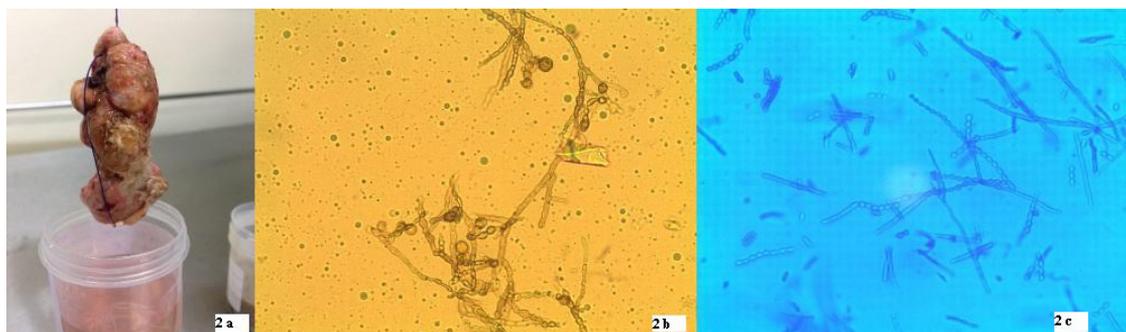


Fig 2(a)–Gross pathology specimen of excised frontal lobe mass. 2(b) Potassium hydroxide wet preparation of the pus from the cerebral abscess showing brown pigmented hyphae with septate round bodies. 2(c) Lacto phenol cotton blue (LCB) wet mount showing oval conidia in long sparsely branched conidiophore.

A provisional diagnosis of cerebral phaeohyphomycosis was made based on the morphological appearance of the brown pigmented hyphae on the unstained KOH wet mount. The patient was put on posaconazole 200mg orally every 8 hours.

After about 6 days fungal colonies with olive grey velvety appearance with a black undersurface was isolated on culture. Lactophenol cotton blue wet mount preparation from the culture showed oval conidia in long sparsely branched conidiophores (Fig 2c). The organism was identified as *C. bantiana* on microscopy by morphology and the fact the fungus grew at 25°C, 37°C and also at 42°C and was urease positive; the last two features distinguishing it from other morphologically similar saprophytic fungi. Identification was confirmed by the Centre for Advance Research in Medical Mycology, WHO Collaborating Centre for Reference and Research of Fungi of Medical Importance, Chandigarh, India. Following surgical excision, the patient's symptoms improved. Her headaches improved and by the fifth post-operative day she was able to walk around the ward on her own without the

risk of falling. She was discharged on the seventh post-operative day and continued on posaconazole. At 6 months follow-up she was doing well without neurological deficits. A follow-up CT scan showed no residual cerebral lesions.

DISCUSSION

The term phaeohyphomycosis is used to denote infections caused by phaeoid (dark colored) septate filamentous moulds that assume mycelial form in the host (Ajello *et al*, 1974). The clinical spectrum includes allergic symptoms, superficial and deep local tissue infections, pulmonary infections, central nervous system infections and disseminated disease (Revankar *et al*, 2004). The neurotropic soil saprophyte *Cladophialophora bantiana* is the most commonly isolated cause of cerebral phaeohyphomycosis (Revankar *et al*, 2004). Apart from the central nervous system (CNS) infection, *C. bantiana* has infrequently caused cutaneous, sub-cutaneous and disseminated disease (Werlinger and Yen-Moore, 2005; Sládekova *et al*, 2014).

In a comprehensive review of CNS phaeohyphomycosis, *C. bantiana* was the

most common pathogen, accounting for 48% of all cases (Revankar *et al*, 2004). CNS infection with *C. bantiana* is nearly always a cerebral abscess; it can cause infection in immunocompromised and non-immunocompromised patients (Revankar *et al*, 2004). There are 11 published reports of CNS infection due to *C. bantiana* among solid organ transplant recipients (Levin *et al*, 2004; Revankar *et al*, 2004; Harrison *et al*, 2008; Sládekova *et al*, 2014).

CNS infections due to *C. bantiana* are rare but often fatal. Among solid organ transplant recipients mortality from *C. bantiana* brain abscess is as high as 71% (Levin *et al*, 2004). The optimum management of this infection appears to be complete excision of the lesion along with long term antifungal prophylaxis.

Complete excision of the lesion is associated with a better outcome than partial excision or aspiration of the abscess through a burr hole (Revankar *et al*, 2004). In a review article by Revankar *et al* (2004), the authors concluded complete excision of CNS phaeohyphomycosis results in better survival (38%) than aspiration or partial excision (14%). In our patient it appears that another center attempted aspiration of the abscess but the abscess returned to its 30mm size within the three months period from the initial burr hole placement until surgery at our institute.

Correct microbiological identification of the causative organism is essential to guide management decisions. Brown pigmented fungal hyphae on a direct KOH wet mount provide a clue to the etiological agent (Li and de Hoog, 2009). Morphological, physiological and biochemical characteristics were used for identification. The colonies were moderately fast growing, olivaceous-grey in color and had a dark under surface. Conidia were pres-

ent in long, sparsely branched, flexuose, acropetal chains from undifferentiated conidiophores. The conidia were unicellular, pale brown, smooth-walled, ellipsoid to oblong-ellipsoid and did not possess the dark pigmented hila present with other *Cladophialophora* species. *C. bantiana* grows at 42°C and is urease positive, features which distinguish it from other morphologically similar saprophytic fungi (Matsumoto and Ajello, 1998).

The optimum antifungal therapy for *C. bantiana* CNS infection is not yet standardized. Limited animal data suggest no benefit with fluconazole or amphotericin B against experimental *C. bantiana* infection (Dixon and Polak, 1987). Although Badali *et al* (2010) found good *in vitro* activity of amphotericin B against *C. bantiana*, clinical experience has shown amphotericin B to be ineffective in many cases of cerebral phaeohyphomycosis (Revankar *et al*, 2004; Roche *et al*, 2005; Hanieh *et al*, 2006; Badali *et al*, 2010). Voriconazole and itraconazole have good activity against these dematiaceous fungi (Revankar *et al*, 2004). The penetration of itraconazole into the CSF is poor (Badali *et al*, 2010). Voriconazole has been used in a number of cases. In one case there was a successful outcome (Lyons *et al*, 2005); failure of voriconazole therapy has also been reported in a number of cases (Fica *et al*, 2003; Levin *et al*, 2004). The drug that appears to have promise is posaconazole, which has apparently good CSF penetration (Badali *et al*, 2010). *In vitro* MIC comparison testing showed posaconazole had the lowest MIC of the antifungals tested (Badali *et al*, 2010). Animal models also found better results with posaconazole against cerebral phaeohyphomycosis by *C. bantiana* compared to fluconazole, itraconazole and amphotericin B (Al-Abdely *et al*, 2005b). Posaconazole has also been

used successfully to treat a cerebral abscess due to *Rhinoctadiella mackenziei* (Al-Abdely *et al*, 2005b). Prior to the report by Al Abdely *et al* (2005b), all eighteen cases reported in the literature during 1983-2004 resulted in mortality despite surgical resection and antifungal therapy (Taj Aldeen *et al*, 2010). Based on these reports we prescribed posaconazole for our patient. Following surgical resection and antifungal therapy with posaconazole the patient remained well without evidence of recurrence after 6 months.

The optimum duration of posaconazole therapy for cerebral phaeohyphomycosis is unclear. Posaconazole is fungistatic not fungicidal. In animal models, the animal succumbed to fungal brain infection when the drug was stopped (Al-Abdely *et al*, 2005b). This raises the possibility of recurrence in our reported case if the drug is discontinued.

A survivor of a *Rhinoctadiella mackenziei* brain abscess was reported to be symptom free for 4 years while taking posaconazole (Al-Abdely *et al*, 2005b). Our patient had completed six months of the antifungal therapy and is continuing therapy with posaconazole.

Posaconazole is well-tolerated and has good oral bioavailability and relatively low toxicity (Pitisuttithum *et al*, 2005). This makes it a good candidate for long term treatment. The addition of flucytosine might be another useful option since it has been reported to have *in vivo* and *in vitro* activity against this pathogen (Revankar *et al*, 2004; Mariné *et al*, 2009). Whether posaconazole should be combined with other antifungals for complete eradication of infection needs further investigations.

In summary, we reported here the case of a cerebral abscess caused by *Clado-*

phialophora bantiana treated successfully with complete excision of the abscess followed by chronic oral treatment with posaconazole. A review of the literature suggests this combination may be the best treatment for this type of case.

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