



# Cerebral phaeohyphomycosis: Importance of early diagnosis and management



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## ABSTRACT

**Introduction:** Phaeohyphomycosis is an infection caused by dematiaceous or pigmented filamentous fungi, which contain melanin in their cell walls. These fungal organisms are neurotropic and are reported to cause cerebral abscesses regardless of the immune status of the patient. The objective of this case report is to emphasize the importance of distinguishing cerebral phaeohyphomycosis from high grade glioma through sufficient microbiological and histopathological studies in order to provide early diagnosis and adequate antifungal therapy if and when cerebral phaeohyphomycosis is diagnosed.

**Case presentation:** This case report describes a 23-year-old male from South East Asia presenting with memory disturbance and cognitive decline with significant improvement in presenting features post-operatively. We illustrate the radiological and clinical similarities between high-grade glioma and fungal brain abscess caused by *Cladophialophora bantiana*. We also discuss the microbiological and histopathological features.

**Conclusion:** The importance of performing microbiological and histopathological testing of the specimen prior to starting the patient on antifungals is emphasized.

**Keywords:** brain abscess, cerebral phaeohyphomycosis, *Cladophialophora bantiana*, fungal infection

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## INTRODUCTION

The first-ever reported case of cerebral phaeohyphomycosis caused by *Cladophialophora bantiana* was in 1911 by Guido Banti and was described by Pier Andrea Saccardo in 1912 as *Torula bantiana*. In 1960, *Torula bantiana* was reclassified as *Cladosporium bantianum*.<sup>1</sup> A morphologically similar species, *Cladosporium trichodes* was reported by Emmons *et al.* in 1952. *Cladosporium trichodes* was discovered to be conspecific in the year 1995 by De Hoog *et al.*<sup>2</sup> Fungal brain abscess incidence is higher among the immunocompromised population. However, cerebral phaeohyphomycosis appear to be caused by neurotropic dematiaceous fungi which are an exception to this rule in more than half the reported cases.<sup>3-5</sup> Dematiaceous fungi are a rare cause of intracerebral abscesses and have high mortality rates of 65 to 73% even with aggressive surgical excision and antifungal medications.<sup>6</sup>

The objective of this case report is to emphasize the importance of distinguishing cerebral phaeohyphomycosis from high grade glioma through sufficient microbiological and histopathological studies in order to provide early diagnosis and adequate antifungal therapy if and

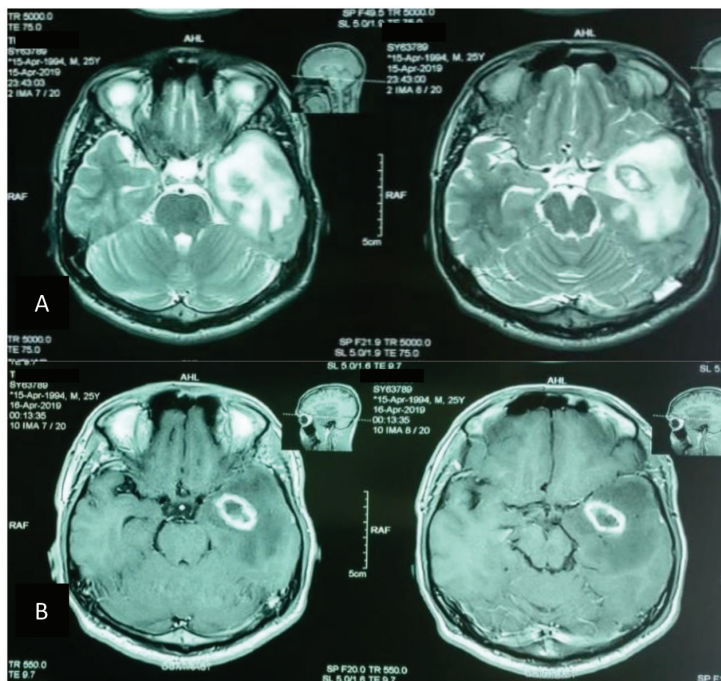
when cerebral phaeohyphomycosis is diagnosed.

## CASE PRESENTATION

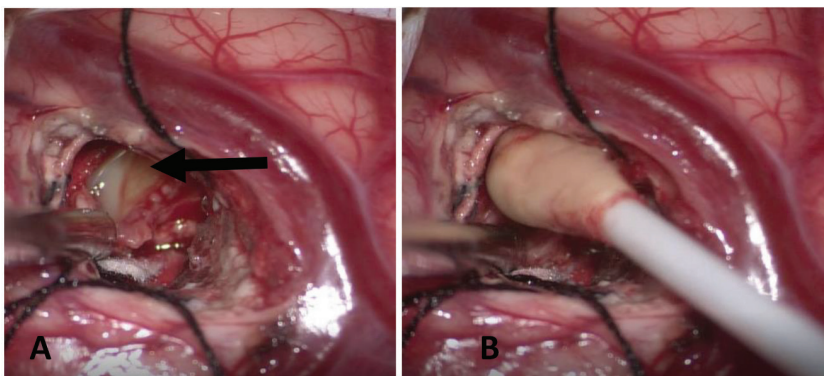
A 23-year-old, final year Microbiology student from South East Asia, a known patient of bronchitis on regular medication, presented with a history of memory disturbance, headache, word-finding difficulty and high-grade fever (Tmax 103° F). Memory disturbance was described as forgetfulness to conversations and names, headache and neck pain of increased intensity and frequency for two weeks prior to the consult. He had mild dysphasia and a significant decline in recall. He tested negative for Human Immunodeficiency Virus, and Hepatitis B surface antigen tests. Brain MRI showed left medial temporal lobe lesion T2 isointense, T1 hypointense, with perilesional edema with enhancing shaggy margins (**Figure 1**). Initial impression was that of a high-grade glioma versus brain abscess.

Intraoperatively, thick-walled abscess with pus was seen (**Figure 2**), and the specimen was sent for histopathologic examination, which showed invasive fungal infection with scattered granulomatous inflammation with necrosis, dematiaceous (pigmented) fungal organisms.

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**Figure 1.** Radiology examination. A. Axial T2 MRI; B. Post-contrast Axial T1 weighted MRI showing left temporal space-occupying lesion with shaggy margins and perilesional edema.



**Figure 2.** Intraoperative images. A. Black arrow showing the pus flowing out from abscess; B. Swab being taken for cultures

Fungal culture studies identified the species as *Cladophialophora bantiana*. Voriconazole assay showed sensitivity to Voriconazole to be  $< 0.5$  uml (Therapeutic range Trough level:  $1.0 - 5.5$   $\mu$ ml) and was started voriconazole. Post-operatively, the patient was noted to have improved cognition with significant improvement in recall.

## DISCUSSION

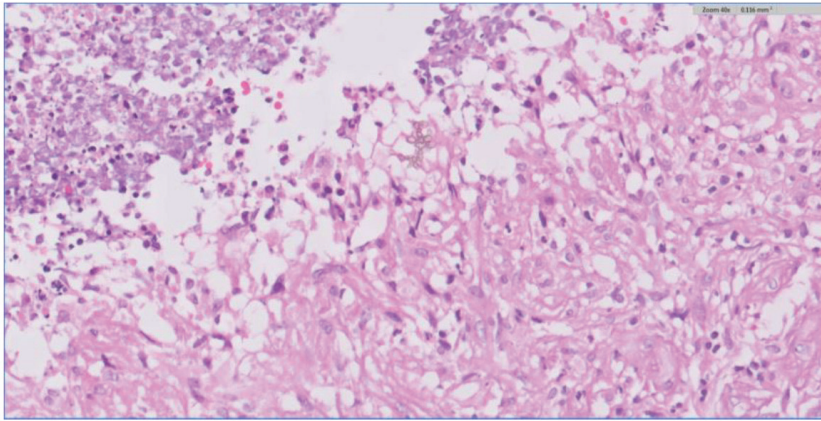
*Rhinocladiella mackenziei* (formerly, *Ramichloridium mackenziei*) is the second most common cause of cerebral phaeohyphomycosis, ranking second to *Cladophialophora bantiana*. The above mentioned two agents are found in soil. Because of this,

occupational predisposition has been reported in agricultural workers, especially farmers, due to the risk of soil exposure. *Cladophialophora bantiana* commonly occurs in the second and third decades of life with male predominance, except *Rhinocladiella mackenziei*, which affects a median age of 62 years with 1:1 male-female ratio of incidence.<sup>7</sup>

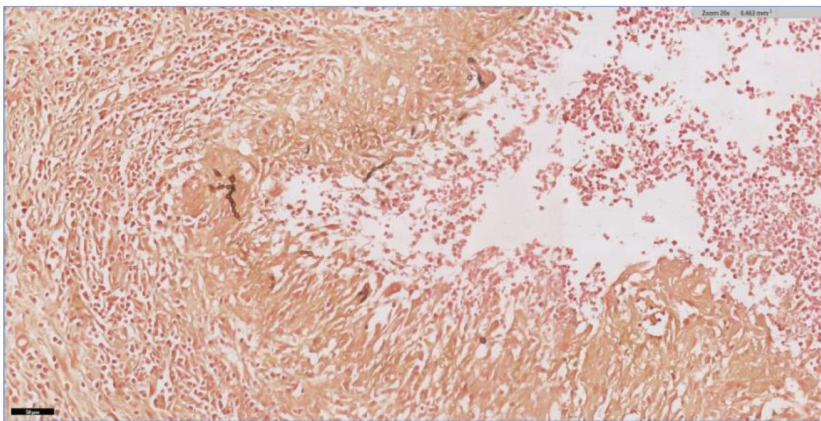
Very few of the reported cerebral phaeohyphomycosis cases occur as a result of traumatic inoculation.<sup>7</sup> Gandham *et al.* concluded that the history of pulmonary infection followed by fungemia could be the cause of spread to the central nervous system.<sup>8</sup> In this case, the patient had a history of chronic bronchitis and was placed on regular medication for bronchitis for one year before the onset of the current set of symptoms. The patient also had a history of working on fungal specimens as part of his training in Microbiology. However, it is hard to determine the route of inoculation. Fungi contain melanin as a virulence factor that works by evading host defence and crossing the blood-brain barrier by binding to hydrolytic enzyme.<sup>4,5</sup>

Hemiparesis and headache are the most common presenting symptoms.<sup>3</sup> Around 70 – 80% of cases typically manifest as a single brain abscess in the frontal lobe (52%),<sup>3</sup> while multiple brain abscesses have been noticed in immunocompromised patients.<sup>4</sup> No particular clinical or laboratory test makes a pre-operative diagnosis of cerebral phaeohyphomycosis possible and depends on histopathologic examination.<sup>9</sup>

The genus *Cladophialophora* (synonymous with *Xylohypha bantiana*; *Cladosporium bantianum*) is characterized by the following: a) the absence of conidiophores, “shield cells,” or prominent hila (attachment points); b) the ability to grow on media containing cycloheximide; and c) having dry, non-fragile chains of conidia.<sup>4</sup> *Cladophialophora bantiana* has been isolated from soil and is likely introduced via inhalation and direct transfer to the brain via the paranasal sinuses, or traumatic head injury.<sup>2</sup> Since the fungus is a true pathogen, laboratory personnel must be made aware that BioSafety Level-3 precautions might be necessary.<sup>7</sup> Colonies are moderately fast-growing, olivaceous-grey, suede-like to floccose and grow at temperatures up to  $42 - 40^{\circ}\text{C}$ .<sup>10</sup> Conidia are formed in long, sparsely branched, flexuose, acropetal chains from undifferentiated conidiophores.<sup>10</sup> Conidia are one-celled (very occasionally two-celled), pale brown, smooth-walled, ellipsoid to oblong-ellipsoid and are  $2 - 3 \times 4 - 7$   $\mu\text{m}$  in size.<sup>10</sup> *Cladophialophora bantiana* may be distinguished from *Cladosporium* species by the absence of conidia with distinctly pigmented hila, the absence of shield cells and by growth at  $> 40^{\circ}\text{C}$  (compared with *Cladophialophora carrionii*, which



**Figure 3.** *Cladophialophora bantiana*, histopathologic description: sections show brain parenchyma with areas of necrosis, neutrophilic microabscesses, aggregates of foamy and epithelioid histiocytes and scattered giant cells forming ill-defined granulomas.



**Figure 4.** *Cladophialophora bantiana*, histopathologic description: slender, irregularly septate hyphae of brown pigmented fungus of phaeohyphomycosis group/dematiaceous type are identified within giant cells, and in tissue fragments along the abscess wall suggestive of invasive fungal infection. The fungal organisms are highlighted by Masson Fontana stain.

has a maximum growth temperature of 35 – 37°C, and *Cladosporium* species, which have a maximum of < 35°C). *Cladophialophora bantiana* may be further distinguished from *Cladophialophora carrionii* by the formation of very long, sparsely branched chains of conidia.<sup>10</sup> **Figures 3 and 4** describe the histopathologic features in this case.

Complete excision of brain lesions may provide better results than simple aspiration unless the lesion is multiple or is located within the eloquent area of the brain. Antifungal agents are generally used in combination with Amphotericin B, 5-flucytosine and itraconazole because it is associated with improved survival rates. Voriconazole can be used as an alternative to itraconazole because of its good penetration into

both CSF and brain tissue. Recommended duration of antifungal therapy is unknown as most of the reported patients expired during treatment except a few survivors who received Voriconazole for about two months. Mortality rate approaches 100% in untreated patients.<sup>7,11-13</sup> Ochiai *et al.* concluded that mortality rate did depend on the immune status of the patient (75% Vs 71%).<sup>14</sup> Jung *et al.* inferred that good general health along with single lesion and aggressive line of management including surgical excision and administration of appropriate antifungal medications are likely to have a better prognosis.<sup>6</sup>

## CONCLUSION

Cerebral phaeohyphomycosis is a rare disease with a high mortality rate despite aggressive surgical excision and antifungals. It is important to distinguish cerebral phaeohyphomycosis from high-grade glioma through sufficient microbiological and histopathological studies to provide early diagnosis and adequate antifungal therapy if and when cerebral phaeohyphomycosis is diagnosed.

## FUNDING

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## CONFLICT OF INTEREST

None

## AUTHORS CONTRIBUTION

All authors did the literature review and wrote the manuscript.

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