

Review Article

Cladophialophora bantiana

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ABSTRACT

Cladophialophora bantiana is one of the few neurotropic fungi which causes CNS infections in immunocompetant hosts. Cerebral phaeohyphomycosis caused by this fungus is one of the most difficult conditions to treat due to its poor prognosis and difficulty in management. Thermo-tolerance and multiple functions of melanin produced by this fungus is responsible for its role as pathogen in immunocompetent hosts. Early recognition and excision of lesion with antifungal therapy are required in the management of this condition. Culture and histopathology aid in the diagnosis. Research to find out a novel cost effective fungicidal agent against C. bantiana is the need of the day.

Keywords: Cladophialophora bantiana, Cerebral phaeohyphomycosis, Immunocompetant hosts

INTRODUCTION

Fungal infections of the central nervous system (CNS) were considered rare until the 1970s. This is no longer true in recent years due to widespread use of corticosteroids, cytotoxic drugs and antibiotics. Immunocompromised patients with underlying malignancy, organ transplantations and acquired immune deficiency syndrome are all candidates for acquiring fungal infections either in the meninges or the brain. A considerable number of cases of CNS fungal infections even in immunocompetent hosts have been reported. One of such infections is Cladophialophora bantiana infection. Cladophialophora bantiana is one among the very few fungi called true neurotropic fungi and one of the most common pathogens causing cerebral phaeohyphomycosis.¹ Cerebral phaeohyphomycosis is one of the most difficult conditions to treat² and poses a threat to the patient and the clinician due to poor prognosis and difficulty in management.³

TAXONOMY

Cladophialophora bantiana belongs to the order Chaetothyrales, family Phaeohyphomycetes and genus Xylohypha.³ Cladophialophora bantiana was formerly called by the names 'Cladosporium trichoides', 'Cladosporium bantianum', 'Xylohypha bantiana' and 'Xylohypha emmonsii'.⁴

MORPHOLOGY AND IDENTIFICATION

The necrotic material with pus-like caseous material from the brain abscess is often the sample sent to the laboratory. Microscopic examination of the KOH preparation reveals numerous septate and darkly pigmented fungal hyphae. Gram and Ziehl-Neelsen smears will not reveal any bacteria or acid fast structures. Sample can be cultured on sabouroud dextrose agar (SDA) plain, SDA with gentamicin, SDA with actidione¹ (Figure 2). Other more commonly used media are potato dextrose agar, oatmeal agar and malt agar. The tubes are incubated at 35°C and 25°C. After 72 hours of incubation, colonies with an olive gray velvety

appearance with a black undersurface are seen. For identification, slide culture is done which shows dark walled septate hyphae with single celled oval conidia in long branched chains (Figure 3). Hyphae are septate and darkly pigmented with many conidia attached to the sides and lying free. Conidia are one-celled, pale brown, smooth-walled, and ellipsoid in shape. The conidiophores showed an acropetous type of branching. *C. bantiana* grows at 42°C and is also urease positive, features which differentiate it from other morphologically similar saprophytic fungi.³



Figure 1: KOH mount showing darkly pigmented fungal hyphae.

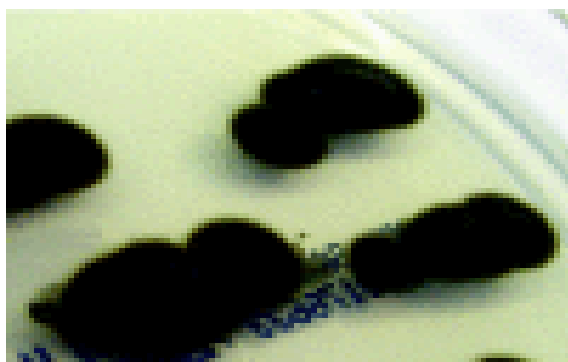


Figure 2: Showing gray black colonies on SDA.



Figure 3: Showing dark walled septate hyphae with oval conidia in long chains.

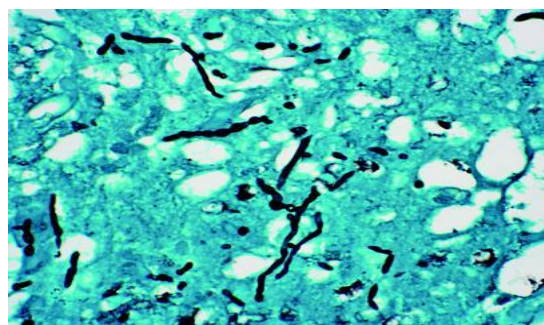


Figure 4: Showing *Cladophialophora bantiana* on fontana masson staining.

Fontana-Masson staining stains it black (Figure 4). The Fontana-Masson stain is specific for melanin. This species is non-proteolytic on casein agar and it is unable to liquefy 12% gelatin.⁵⁻⁷ In all cases for which histopathologic findings were reported, the presence of hyphae was noted, although granulomatous inflammation was noted in only some cases.⁴ Hence culture and histopathology aid in its diagnosis. However, molecular methods like sequencing are the most dependable tools which can be used for its confirmation.³

PATHOGENESIS

This fungus primarily colonizes in the lung from where it is transferred through the haematogenous route to the CNS. The multiple brain abscesses which are seen frequently due to this fungus also suggest its dissemination through the blood stream.⁸ It has been implicated as a leading cause of cerebral phaeohyphomycosis because of its affinity to glial tissue. There are two important virulence factors responsible for its pathogenicity i.e. melanin production and tolerance to heat above 40°C. Melanin confers a protective advantage by scavenging free radicals and hypochlorite that are produced by phagocytic cells and that would normally kill most organisms.^{9,10} Melanin also binds to hydrolytic enzymes preventing their action on the plasma membrane. These multiple functions explain the pathogenic potential of these fungi, even in immunocompetent hosts.¹¹

CEREBRAL PHAEOHYPHOMYCOSIS

Most reported infections of the central nervous system (CNS) caused by this entity occur in the cerebrum, with a few documented cases of cerebellar infection.¹² It most often manifests as brain abscesses in immunocompetent people, however meningitis and myelitis were observed in a limited number of cases.¹³ The brain infection may present as a solitary, well-defined abscess, multiple abscesses or poorly demarcated cerebritis with extensive necrotic lesions.^{4,14-17} Brain abscess is the commonest manifestation.⁴ The abscesses are usually hemispheric and they affect the white matter and show a predilection for the frontal lobes. However, choroid plexus, thalamic, diencephalic, and cerebellar involvement can also

occur.¹⁸ The extent and delineation of the lesions may vary according to the immune status and immune response of the subject.⁵

EPIDEMIOLOGY

Males are affected more frequently, with ages of onset ranging from 6 to 76 years (mean age, 37 years).¹² Most patients are immunocompetent at the time of infection.¹⁹ The fungus has no ethnic or geographic predilection; it is found in decaying vegetation, wood, and soil.²⁰ In one series, 44% of patients had a history of traumatic or inhaled exposure to soil.¹⁹

TREATMENT

The treatment of the cerebral phaeohyphomycosis is not successful in most cases, due to cellular immune deficiencies, diagnostic delays and sometimes the presence of multiple brain abscesses that turns difficult the surgical approach. However, some publications have reported a successful treatment in immunocompetent^{21,22} and immunocompromised patients.²³ Antifungal therapy is essential in spite of surgical excision as residual fungal elements cannot be ruled out even after a thorough excision.²⁴ Posaconazole and itraconazole have the best *in vitro* activity against *C. bantiana*. But adverse effects and lack of formulations of itraconazole has limited its use.¹⁶ Posaconazole is a promising drug for cerebral phaeohyphomycosis but is not fungicidal.^{25,26} Innate resistance of Amphotericin B and fluconazole limit their use though Amphotericin has some activity against this fungus. Fluconazole has limited activity but because of its low cost is preferred in some cases.²⁷ However monotherapy is not recommended in these cases.²⁸ Liposomal Amphotericin B and a high dose azole like posaconazole can be considered for the management of cerebral phaeohyphomycosis after excision of the abscess.²⁹ However the cost of therapy would be approximately a huge amount of Rs 6,00,000 and in spite of this we would not be able to guarantee survival to the patient. The role of echinocandins and nikkomycins in the treatment of cerebral phaeohyphomycosis is unclear at present.³⁰ There is undoubtedly a need for further research to find out a novel cost-effective fungicidal agent to which *Cladophialophora bantiana* is sensitive.

CONCLUSION

Cladophialophora bantiana should be carefully looked for in CNS infections as nonavailability of effective and affordable medical treatment, variable success & fatal outcome demand early recognition and excision of lesion to save the patient. Though posaconazole appears to give promising results in these infections it is not a fungicidal drug. There is a need for further research to find out a novel cost-effective antifungal agent to which *Cladophialophora bantiana* is sensitive.

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