Melanized Fungi in CNS Infections

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Abstract

There are increasing reports of central nervous system infections due to melanized fungi worldwide. These brown pigment-containing fungi are often grouped under dematiaceous mycosis or phaeohyphomycosis. They are predominantly responsible for cerebral infections and brain abscesses, *Cladophialophora bantiana, Exophiala dermatitidis, and Phialophora*. Fungi under the *Bipolaris genus are found in* immunocompetent individuals who present with a chronic sinusitis which aggravates into secondary cerebral infection. The vehicle of transmission of phaeohyphomycosis is usually of exogenous nature, e.g., thorn/wood pricks. The melanin-like pigment found in their cell walls is responsible for immune evasion mechanisms. These golden-brown pigments can assist in making a presumptive diagnosis based on their microscopic visualization when examining histopathology samples. There are also cases of hematogenous spread leading to central nervous system involvement, due to penetrating head injuries and direct spread. *Curvularia* is a melanized mold found ubiquitously in soil, which although extremely rare, has the potential to cause life-threatening brainstem infection.

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Keywords

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16.1 Introduction

The central nervous system (CNS) is more privileged than other organ systems from infections because of anatomical and physiological barriers like blood, brain, and cerebrospinal fluid (CSF). Even though CNS infections are not as common as lung or kidney infections, there has been an increase in the rate of CNS infections in the past few decades owing to several reasons for decreasing immunity status. Though CNS infections are uncommon, they result in unprecedented mortality and morbidity. They significantly impact the quality of life of the affected individual as a residual disability, even if nonfatal. Therefore, there is a merit in understanding of and detailed accounts of CNS infections.

Usually, CNS infections are encountered as opportunistic infections and primary infections primarily by bacteria or viruses. Tuberculosis is a significant burden in poor socioeconomic status and is mainly endemic in regions of southeast Asia and Africa and rarely seen in the west. Further rare are the fungal infections of the CNS, and CNS mycoses often result in decreased systemic immunity. Unlike other infections, several classes of fungus can infect the CNS, and the site, severity, underlying disease, and clinical course differ according to the fungal species (Perfect and Durack 1997). The present chapter focuses on melanized fungi in CNS infections where melanization of the fungi is the primary feature either as phenotypic appearance or in the histology.

As we recognize that the field will continue to develop and broaden as a result of our growing understanding of and experience with these clinically significant fungi, our goal is not to review every publication on melanized fungi but rather to provide a comprehensive but in-depth overview of the field as it stands at the moment. We will be restricting the present chapter to CNS melanized fungi clinical aspects as the details on the ecology, classification, taxonomy, nomenclature, and identification shall be covered in other chapters.

16.2 Melanized Fungi

Melanin is a highly stable molecule resistant to damage by the physicochemical processes owing to its molecular structure. Its role in the pathogenesis of several fungi has been explained in detail in several studies (Bloomfield and Alexander 1967; Casadevall et al. 2000; Gómez and Nosanchuk 2003; Jacobson 2000; Liu and Nizet 2009; Nosanchuk and Casadevall 2003). Melanocytes produce melanin by oxidation of the amino acid tyrosine, followed by its polymerization. There are several mechanisms by which melanin provides unique protective features to fungal

agents. For example, melanin may protect the fungi from harmful ionizing radiations, heat and cold shock, and chelating metal ions that may be toxic to the fungal cells (Hong and Simon 2007; Pacelli et al. 2017; Cordero et al. 2018; Khajo et al. 2011; Wang and Casadevall 1994). There have been changes in the terms used to denote melanized fungi. *Sporothrix schenckii* was one of the oldest melanized fungi, and later, all the fungi with similar characteristics were termed "Sporotrichoid." However, the gradually more useful term "Phaeooid" represents melanized fungi. Phaeo is a Greek term that means dark. For example, phaeohyphomycoses means infection by dark-walled fungi. Some people also use the word "dematiaceous" for melanized fungi; however, others mention that "dematiaceous" is a misnomer as the Greek phrase "deme" means bundle (Pappagianis and Ajello 1994).

There is confusion about grouping a fungal agent as melanized fungi. This is because melanin has been found to some extent in almost all clinically significant fungi like *Histoplasma capsulatum*, *Paracoccidioides brasiliensis*, *Aspergillus* spp., and even *Candida albicans* as there is no reliable method to quantify the amount of the melanin in the fungus. Therefore, some people advocate that the term melanized fungi should be reserved for the fungus with brown-pigmented hyphae in the tissue seen without any staining. Melanized fungi are commonly present in the environment; still, the infection tends to be rare. Most cases of infections by melanized fungi occur as opportunistic infections; however, there are reports of fatal infections in individuals with normal immunity (Revankar et al. 2002, 2004).

The clinical syndromes caused by the melanized fungi are classified as eumycetoma, Chromoblastomycosis, and Phaeohyphomycosis based on histological appearance. Eumycetoma and Chromoblastomycosis have a small number of fungi that result in deep tissue infection in lower extremities and tropical environments, respectively (Pang et al. 2004; Mcginnis 1983).

The phaeohyphomycoses are the fungal infections not covered by the earlier two (Revankar 2006). Melanized CNS fungal infections are covered under the umbrella term of Phaeohyphomycosis. Fungal agents cause Rhinocerebral Phaeomycosis under the Ascomycetes order Pleosporales, the pathogens on the grasses and spread by the air.

16.3 Melanized CNS Fungal Infections

Revankar et al. reported a review of 101 cases from 1966 to 2002 of melanized fungal CNS infections in 2004. They found that the brain abscess was the most common presentation; more than half had normal immunity, and the outcome was poor with mortality >50% irrespective of the individual's immune status (Revankar et al. 2004). In the review, the authors found that the most frequently isolated species for primary CNS melanized fungal infection was *Cladophialophora bantiana*, followed by *Ramichloridium mackenziei* (found exclusively in patients from the middle east) (Revankar et al. 2004). Other predominant species that cause primary CNS melanized fungal infection were *Ochroconis gallopava*, *Bipolaris spicifera*,

Exophiala dermatitidis, and *Chaetomium strumarium* (Revankar et al. 2004; Hong and Simon 2007; Chakrabarti 2007).

Secondary infections are due to grass-inhabiting species and secondary to chronic fungal sinusitis. They include *Bipolaris*, *Dissitimurus*, *Exserohilum*, *Curvularia lunata*, *Cladosporium cladosporioides, Nodulisporium species, and Pleosporaceae* (Hong and Simon 2007). The authors further found that though most of the cases occurred in the rural settings, there was no specific exposure in individual patients. Several other melanized fungal CNS infections were reported in the last two decades, and a new species, *Fonsecaea monophora,* was identified with a preference for the central nervous system.

16.4 Pathophysiology

There are animal models that illustrate CNS infection with melanized fungi in immunocompromised rats (Al-Abdely et al. 2005b; Dixon et al. 1987). However, it is not clear why some melanized fungi prefer the central nervous system in individuals with normal immunity. The route of CNS spread could be nasal and paranasal sinuses in immunocompromised individuals. In immunocompetent individuals, the primary route of CNS infection is thought to be due to the hematogenous spread from subclinical pulmonary infective foci.

The most common neurotropic melanized fungal species belong to the *Herpotrichiellaceae* and are acquired by inhalation and then rapidly disseminate to the CNS via the hematogenous spread. However, the exact route of CNS infection in immunocompetent individuals is difficult to describe because of the long asymptomatic period. The author's source is iatrogenic infection reported in contaminated steroid epidural injection with mortality>60%. Centers for Disease Control and Prevention (CDC) (2002) However, certain infections seem to have come about as a result of hematogenous spread, direct inoculation from penetrating head trauma, and through contaminated wounds.

Most CNS infections are believed to be secondary to extension from paranasal sinuses. (Skovrlj et al. 2014) Pleosporales has large conidia that cannot enter the lungs and get trapped in the sinuses and result in allergic sinusitis with gradual increase in the fungal ball and extended polyposis. As the conidia geminate in the sinus and due to pressure erosion of the bony wall of the sphenoid and ethmoid sinus due to chronic sinusitis, these are secondary cerebral infections. However, the above-mentioned route for the cerebral infection is rare; it has high fatality rate. Another difference between Rhinocerebral phaeomycosis and cerebral Phaeohyphomycosis is that the agents in the first one are grass pathogens and cause secondary cerebral infection. At the same time, in the latter, they are predominantly neurotropic fungi and are thought to reach the CNS via the hematogenous route. It is also believed that causative agents are fungi adapted to spend some part of their life cycle in the vertebrates in cases of cerebral Phaeohyphomycosis.

16.5 Clinical Manifestations

In the identified species causing the melanized fungal CNS infection, brain abscess was the most commonly identified presentation with standard treatment protocols. Excision tends to yield better results than the simple aspiration of the abscess (Revankar et al. 2004). The usual clinical presentation consisted of headache, seizures, and neurological deficits depending on the cortical location of the fungal lesion. In these cases, the mortality was >70% (Revankar et al. 2004). However, in patients with features of encephalitis and diffuse brain involvement, the mortality reported is as high as 100% (Abbott et al. 1995; Biggs et al. 1986). Meningitis is also reported in several reports of melanized fungal infection and is difficult to treat and associated with high mortality rates (Al-Aidaroos et al. 2007; Banerjee et al. 2002). Apart from this, there are reports of patients presenting with low backache (Shrivastava et al. 2017). Shrivastava et al. reported a middle-aged farmer who complained of low back ache and decreased urinary sensation. On neuroimaging, they found epidural collection with intrathecal extension from the D10-L2 vertebra causing spinal stenosis and compressing the cauda equina nerve roots. The authors identified the species as *Curvularia lunata* and successfully treated the patient with laminectomy and surgical excision and a combination of voriconazole and liposomal amphotericin B (Shrivastava et al. 2017).

16.6 Diagnosis

The diagnosis of Phaeohyphomycosis or neurological infections by melanized fungi depends on the clinical correlation with radiological evidences, sample as tissue or CSF analysis for direct microscopy, culture isolation, processing of culture for fungal genus, and species identification (Figs. 16.1, 16.2, 16.3, 16.4, 16.5 and 16.6). In case of difficulty in speciation by conventional methods, molecular confirmation is required for choice of treatment modality.

Molecular confirmation is the only and definitive diagnostic method for nonsporulating melanized fungus.

16.7 Medical Management

Combination therapy is more effective than monotherapy (Garg et al. 2007). There have been several reports on different treatment modules for melanized CNS infections; however, it is unclear if they are effective. There is no consensus on optimal antifungals to be used in these infections. The reported antifungals include amphotericin B, flucytosine, itraconazole, and Posaconazole (De Lastours et al. 2003; Nesky et al. 2000; Revankar et al. 2004). There are even reports of failure of medical management with the above-mentioned antifungals and it is suggested to use a combination of these antifungals (Levin et al. 2004; Lyons et al. 2005). In an animal study, it was found that the addition of flucytosine to the Posaconazole and

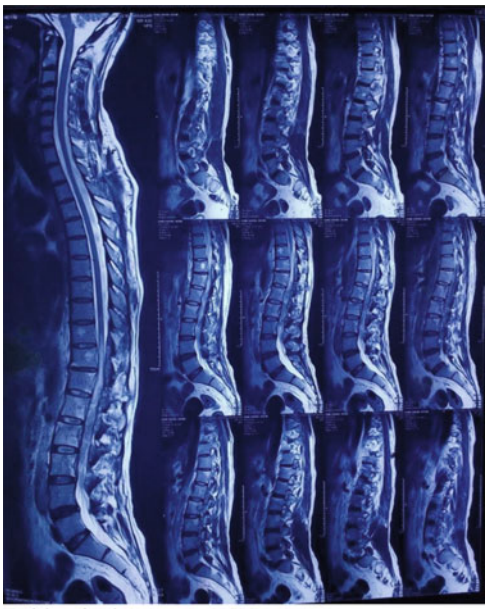

Epidural Abscess on MRI

Fig. 16.1 Epidural abscess on MRI

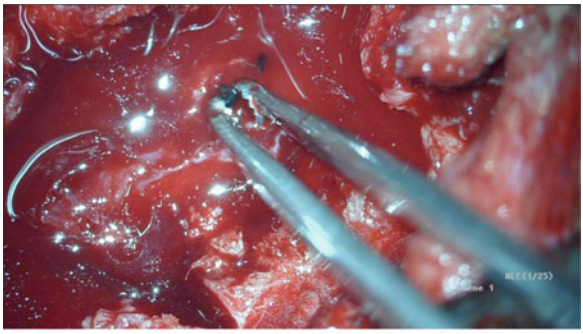
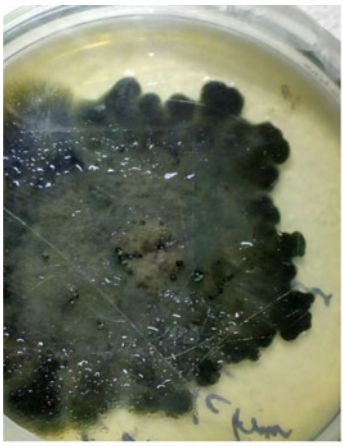

Epidural abscess showing blackish soft material

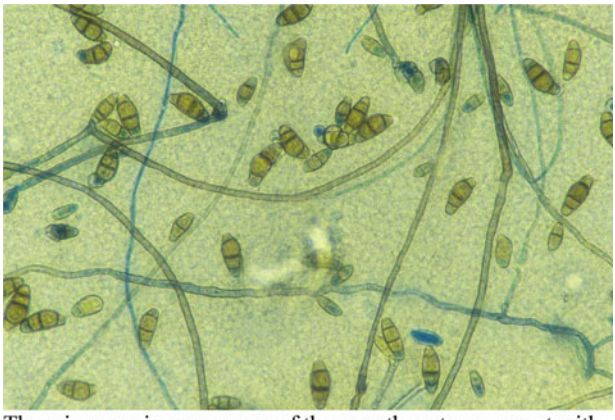
Fig. 16.2 Epidural abscess showing blackish soft material

micafungin had better outcome than other antifungals in infection with *Cladosporium bantana* (Mariné et al. 2009). Studies with long-term follow-up of cerebral phaeohyphomycosis caused by *Ramichloridium mackenziei* species have shown 100% mortality. Al-abdely et al. reported successful treatment in a 62-year-old patient post-renal transplant and cerebral abscess by *Ramichloridium mackenziei* with posaconazole oral suspension, 800 mg/day, in divided doses after the failed treatment and recurrent lesion after therapy with liposomal amphotericin B, itraconazole, and 5-flucytosine (Al-Abdely et al. 2005a).



Sabouraud dextrose agar from the black material with tissue from epidural space showing Olive green growth with black pigment on reverse.

Fig. 16.3 Sabouraud dextrose agar from the black material with tissue from epidural space showing olive green growth with black pigment on reverse



The microscopic appearance of the growth on tease mount with Lactophenol cotton blue shows melanized and hyaline fungal hyphae with brownish curved distoseptate conidia with three transverse septation and third cell enlarged suggestive of a melanized fungus *Curvularia lunata.*

Fig. 16.4 The microscopic appearance of the growth on tease mount with Lactophenol cotton blue shows melanized and hyaline fungal hyphae with brownish curved distoseptate conidia with three transverse septation and third cell enlarged suggestive of a melanized fungus *Curvularia lunata*

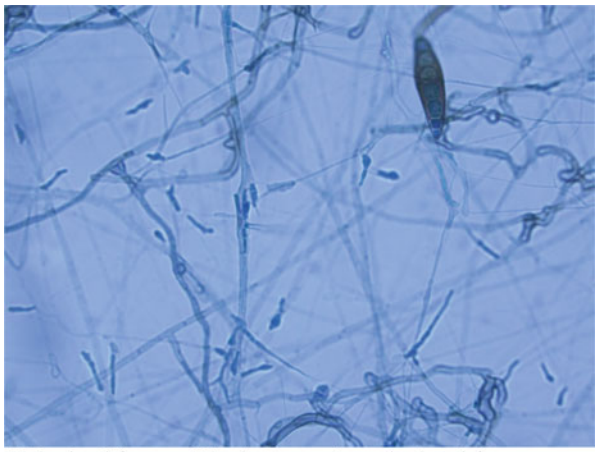


Fig. 16.5 Melanized fungus *Bipolaris cactivora* isolated from temporal lobe involvement

Melanized fungus *Bipolaris cactivora* isolated from temporal lobe involvement.

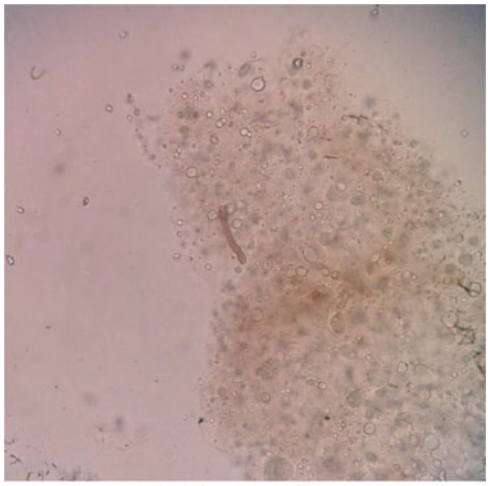


Fig. 16.6 Melanized hyphal fragment in tissue sample observed on direct microscopy by 20% potassium hydroxide

Melanized hyphal fragment in tissue sample observed on direct microscopy by 20% potassium hydroxide.

16.8 Surgical Management

According to the reported literature, complete excision of the abscess was more fruitful than partial excision and aspiration. A retrospective series on 10 cases of CNS cladosporiosis from south India spanning three decades in immunocompetent individuals found that nine had space-occupying mass lesions, while one patient presented with features of chronic meningitis (Garg et al. 2007). The authors further

reported that the mortality was 50%, and patients who underwent burr hole and aspiration of abscess required excision of the abscess. The complete excision of the abscess had better outcomes than the aspiration or the partial excision of the abscess (Garg et al. 2007). In contrast, Delfino et al. reported a case of CNS cladosporiosis that was cured after repeat surgical excision of the abscess, despite the delayed and inappropriate primary therapy (Delfino et al. 2006).

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