Phaeohyphomycosis: Infection Due to Dark (Dematiaceous) Molds

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Introduction

Dematiaceous, or darkly pigmented fungi are a large, heterogeneous group of organisms that have been associated with a wide variety of clinical syndromes. These are uncommon causes of human disease, but can be responsible for life-threatening infections in both immunocompromised and immunocompetent individuals. In recent years, these fungi have been increasingly recognized as important pathogens and the spectrum of diseases they are associated with has also broadened.

The clinical syndromes caused by the dark-walled fungi are typically distinguished based on characteristic histologic findings into chromoblastomycosis, mycetoma, and phaeohyphomycosis. Chromoblastomycosis and mycetoma are caused by a small group of fungi that are associated with characteristic structures in tissues and are usually seen in tropical areas [1]. These are discussed in Chap. 22 (Fungal Infections of Implantation). Phaeohyphomycosis is a term introduced by Ajello et al. in 1974, which literally means "infection caused by dark-walled fungi" [2]. It is a catch-all term generally reserved for the remainder of clinical syndromes caused by dematiaceous fungi that range from superficial infections and allergic disease to brain abscess and widely disseminated disease [3]. These fungi are alternately called phaeoid, dematiaceous, dark, or black molds. While typically, phaeohyphomycosisis a term limited to infections caused by the dark molds, there are dark yeasts that rarely cause infection, and these are also included under this grouping by many experts.

Etiologic Agents

More than 150 species and 75 genera of dematiaceous fungi have been implicated in human disease [4]. The common characteristic among these fungi is the presence of melanin in their cell walls, which imparts the dark color to their conidia or spores and hyphae. Their colonies are typically brown to black in color as well. As the number of patients immunocompromised from diseases and medical therapy increases, additional species are being reported as causes of human disease, expanding an already long list of potential pathogens. Common genera associated with specific clinical syndromes are listed in Table 12.1.

Guidelines are available for the handling of potentially infectious fungi in the laboratory setting. Cultures of certain well-known pathogenic fungi, such as *Coccidioides immitis* and *Histoplasma capsulatum,* are suggested to be worked with in a Biosafety Level 3 facility, which requires a separate negative pressure room. Recently, certain agents of phaeohyphomycosis, in particular *Cladophialophora bantiana,* have been included in the list of fungi that should be kept under Biosafety Level 2 containment [5]. This seems reasonable given their propensity, albeit rarely, for causing life-threatening infection in normal individuals.

Epidemiology

These fungi are typically soil organisms and generally distributed worldwide [6]. However, there are species that do appear to be geographically restricted, such as *Ramichloridium mackenzei,* which has only been seen in patients from the Middle East [7]. Exposure is thought to be from inhalation or minor trauma, which may not even be noticed by the patient. Anecdotal reports suggest that smoking may be a risk factor in patients who are immunodeficient [8]. Surveys of outdoor air for fungal spores routinely observe dematiaceous fungi [9]. This suggests that most if not all individuals are exposed to them, though they remain uncommon causes of

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Table 12.1 Clinical spectrum and treatment of phaeohyphomycosis

Clinical syndrome	Commonly associated fungi	Therapy
Onychomycosis	*Onychocola*, *Alternaria*	Itraconazole or terbinafine
Subcutaneous nodules	*Exophiala*, *Alternaria*, *Phialophora*	Surgery ± itraconazole or voriconazole
Keratitis	*Curvularia*, *Bipolaris*, *Exserohilum*, *Lasiodiplodia*	Topical natamycin ± itraconazole or voriconazole
Allergic fungal sinusitis/Allergic broncho-pulmonary mycosis (disease)	*Curvularia*, *Bipolaris*	Corticosteroids ± itraconazole or voriconazole
Pneumonia	*Ochroconis*, *Exophiala*, *Chaetomium*	Itraconazole or voriconazole (amphotericin B if severe)
Brain abscess	*Cladophialophora* (*C. bantiana*), *Ramichloridium* (*R. mackenzei*), *Ochroconis*	See text
Disseminated disease	*Scedosporium* (*S. prolificans*), *Bipolaris*, *Wangiella*	See text

disease. These fungi may also be found to be contaminants in cultures, making the determination of clinical significance problematic. At one institution, only 10% of positive cultures were associated with clinical disease [10]. A high degree of clinical suspicion as well as correlation with appropriate clinical findings and histopathology is required when interpreting culture results.

Pathogenesis and Immunology

Little is known regarding the pathogenic mechanisms by which these fungi cause disease. One of the likely virulence factors is the presence of melanin in the cell wall, which is common to all dematiaceous fungi. It may confer a protective advantage by scavenging free radicals that are produced by phagocytic cells in their oxidative burst that normally kill most organisms [11]. In addition, melanin may bind to hydrolytic enzymes, thereby preventing their action on the plasma membrane [11]. In the yeasts *Cryptococcus neoformans* and *Wangiella dermatitidis,* disruption of melanin production leads to markedly reduced virulence in animal models [12, 13]. Melanin has also been associated with decreased susceptibility of fungi to certain antifungals, possibly by binding these drugs [14, 15]. It is interesting to note that almost all allergic diseases and eosinophilia are caused by two genera, *Bipolaris* and *Curvularia,* though the virulence factors responsible for eliciting allergic reactions are unclear at present [16].

Clinical Manifestations

Superficial Infections

Superficial infections are the most common form of disease associated with phaeohyphomycosis. These may be divided into tinea nigra, onychomycosis, subcutaneous lesions, and keratitis and are generally associated with minor trauma or other environmental exposure. Although many pathogens have been reported, relatively few are responsible for the majority of infections.

Tinea nigra is primarily seen in tropical areas, and involves only the stratum corneum of the skin. Patients are generally asymptomatic, presenting with brownish-black macular lesions, almost exclusively on the palms and soles. *Hortaea werneckii* is the most commonly isolated species, though *Stenella araguata* has also been cultured from lesions [17]. Tinea nigra may be confused with a variety of other diseases, including dysplastic nevi, melanoma, syphilis, or Addison's disease. Diagnosis is made by scrapings of lesions and culture. As it is a very superficial infection, simple scraping or abrasion can be curative, though topical treatments such as keratolytics or imidazole creams are also highly effective [17].

Dematiaceous fungi are rare causes of onychomycosis, and the term fungal melanonychia has been used to describe this entity, which is seen predominantly in tropical regions [18]. Clinical features may include a history of trauma, the involvement of only one or two toenails, and the lack of response to standard systemic therapy [19]. Twenty-one species have been implicated as causes, including *Alternaria, Curvularia,* and *Scytalidium* have been reported, with the latter being highly resistant to therapy [18].

There are numerous case reports of subcutaneous infection due to a wide variety of species [20, 21]. Minor trauma is the usual inciting factor, though it may be unrecognized by the patient. Lesions typically occur on exposed areas of the body and often appear cystic or papular. Immunocompromised patients are at increased risk of subsequent dissemination. Occasionally, these infections may involve joints or bone.

Fungal keratitis is an important ophthalmologic problem, particularly in tropical areas of the world. In one large series, 40% of all infectious keratitis was caused by fungi, almost exclusively molds [22]. The most common fungi are *Fusarium* and *Aspergillus,* followed by dematiaceous fungi (up to 8–17% of cases) [23]. Approximately, half of the cases are associated with trauma; prior eye surgery, diabetes, and contact lens use have also been noted as important risk factors

[23]. In a study from the USA of 43 cases of *Curvularia* keratitis, almost all were associated with trauma [24]. Plants were the most common source, though several cases involving metal injuries were seen as well.

Allergic Disease

Relatively few species have been associated with allergic disease. *Alternaria alternata* is thought to be involved in some cases of asthma [25]. Whether dematiaceous fungi may be responsible for symptoms of allergic rhinitis is unclear, as it is difficult to quantitate exposure and to distinguish them from other causes [26].

Bipolaris and *Curvularia* are responsible for most cases of allergic fungal sinusitis (AFS) and allergic bronchopulmonary mycosis (ABPM). Patients with AFS usually present with chronic sinus symptoms that are not responsive to antibiotics. Previously, *Aspergillus* was thought to be the most common fungus responsible for allergic sinusitis, but it is now appreciated that disease due to dematiaceous fungi actually comprises the majority of cases [27]. Criteria suggested for this disease include (1) nasal polyps, (2) the presence of allergic mucin, containing Charcot–Leyden crystals and eosinophils, (3) hyphal elements in the mucosa without the evidence of tissue invasion, (4) positive skin test to fungal allergens, and (5) on computed tomography (CT) scans, characteristic areas of central hyperattenuation within the sinus cavity [28]. Diagnosis generally depends on the demonstration of allergic mucin, with or without actual culture of the organism.

Allergic bronchopulmonary mycosis (ABPM) (or disease (ABPD)) is similar in presentation to allergic bronchopulmonary aspergillosis (ABPA), which is typically seen in patients with asthma or cystic fibrosis [29]. Criteria for the diagnosis of ABPA in patients with asthma include: (1) asthma, (2) positive skin test for fungal allergens, (3) elevated IgE levels, (4) *Aspergillus*-specific IgE, and (5) proximal bronchiectasis [30]. Similar criteria for ABPM are not established, but finding allergic mucin (Charcot–Leyden crystals and eosinophils) without tissue invasion, as in AFS, makes this diagnosis highly likely [31].

Pneumonia

Nonallergic pulmonary disease is usually seen in immunocompromised patients, and may be due to a wide variety of species, in contrast to allergic disease [16, 31–34]. Clinical manifestations include pneumonia, asymptomatic solitary pulmonary nodules, and endobronchial lesions which may cause hemoptysis.

Brain Abscess

This is a rare, but frequently fatal manifestation of phaeohyphomycosis [35]. Interestingly, over half of the reported cases have occurred in patients with no risk factors or known immunodeficiency. Lesions are usually solitary. Symptoms may include headache, neurologic deficits, and seizures, though the classic triad seen in bacterial brain abscess (fever, headache, and focal neurologic deficit) is not usually present. The most commonly isolated organism is *Cladophialophora bantiana*, particularly in immunocompetent patients. The pathogenesis may be hematogenous spread from an initial, presumably subclinical pulmonary focus. However, other risk factors such as chronic sinusitis or smoking have been implicated in case reports [8, 36]. It remains unclear why these fungi preferentially cause central nervous disease (CNS) disease.

Disseminated Infection

This is the most uncommon manifestation of infection seen with dematiaceous fungi. Most patients are immunocompromised, though occasional patients without known immunodeficiency or risk factors have developed disseminated disease as well [37]. In contrast to most invasive mold infections, blood cultures are often positive. The most commonly isolated fungus, *Scedosporium prolificans,* may also be associated with septic shock. Peripheral eosinophilia, seen in 11 % of cases, is more commonly associated with *Bipolaris* or *Curvularia*.

Diagnosis

In contrast to other common mycoses that cause human disease, there are no specific serologic or antigen tests available to detect these fungi in blood or tissue. However, the nonspecific serum 1,3-β-D-glucan test may be positive in certain cases of invasive disease [38], and certain species have been demonstrated to contain the *FKS* gene responsible for its production [39]. The diagnosis of phaeohyphomycosis currently rests on pathologic examination of clinical specimens and careful gross and microscopic examination of cultures (Fig. 12.1). Hospital laboratories can generally identify the most common genera associated with human disease (Fig. 12.2), though referral to a reference laboratory is often needed to identify unusual species. As many of these are rarely seen in practice, a high degree of clinical suspicion is required when interpreting culture results. Increasingly, molecular techniques such as internal transcribed sequence (ITS) sequencing are being used to definitively identify

Clinical Suspicion

↓

Obtain clinical material

(tissue, blood, aspirate, etc.)

↙ ↘

Microscopic examination

↙ ↘

Culture

Macroscopic - observe for darkly pigmented colonies

Microscopic - identify by morphology (hyphae, yeasts, conidia)

Direct observation

Observe for fungal elements with dark cell walls

Histopathology

Observe for irregular hyphae and beaded yeast-like forms; positive staining by Fontana-Masson method

Fig. 12.1 Diagnostic approach for phaeohyphomycosis

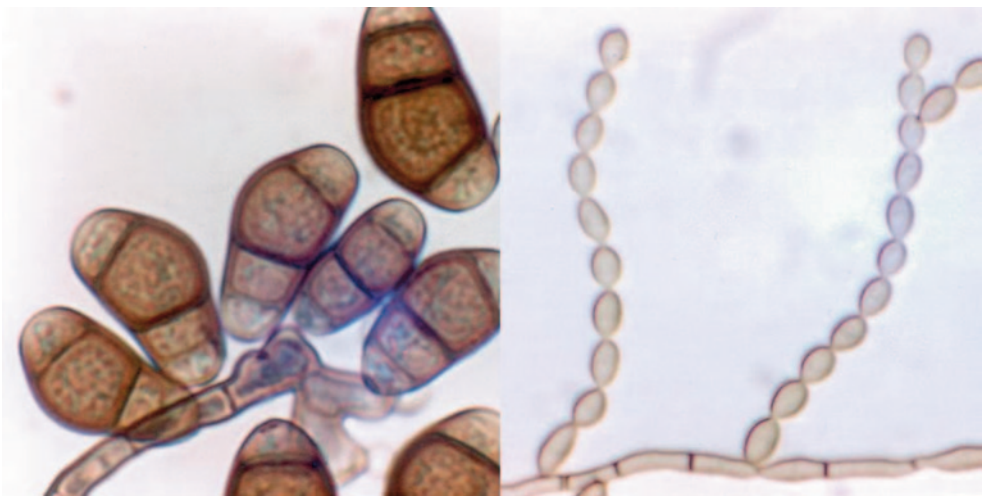

Fig. 12.2 Commonly seen fungi causing phaeohyphomycosis. *Left panel*, *Curvularia lunata*; *right panel*, *Cladophialophora bantiana*

isolates to the species level and are becoming the standard to distinguish between closely related strains and establish novel species [4].

In tissues, these fungi stain strongly with the Fontana-Masson stain, which is specific for melanin (Fig. 12.3) [3]. This can be helpful in distinguishing these fungi from other species, particularly *Aspergillus*. In addition, hyphae typically appear more fragmented in tissue than seen with *Aspergillus,* with irregular septate hyphae and beaded, yeast-like forms [3].

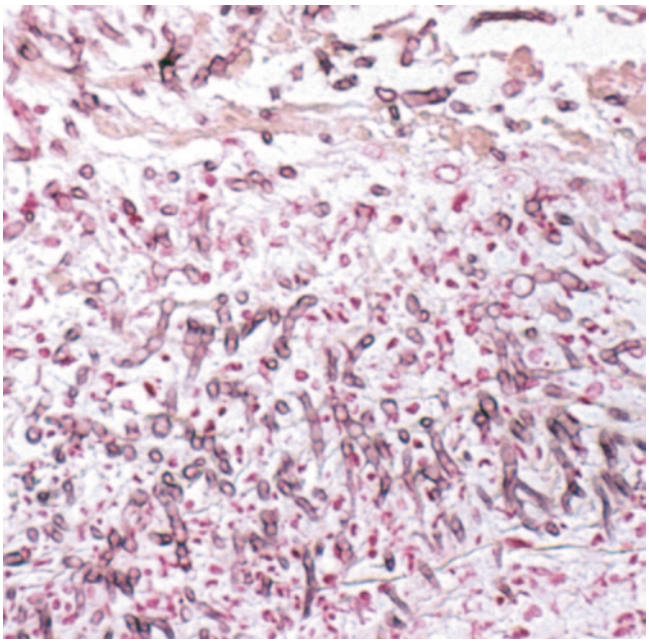

Fig. 12.3 Fontana-Masson stain of *Bipolaris* infection in the lung, demonstrating irregular hyphae and beaded yeast-like forms

Treatment

Therapy is not standardized for any of these clinical syndromes, and randomized trials are unlikely given the sporadic nature of cases. Itraconazole, voriconazole, and posaconazole demonstrate the most consistent in vitro activity against this group of fungi, though far more clinical experience has accumulated with itraconazole [40]. Isavuconazole is a novel triazole with good in vitro activity, though it is not yet approved for use [41, 42]. Amphotericin B may be used for severe infections in unstable patients; high doses of lipid formulations may have a role in the treatment of refractory cases or in patients intolerant of standard amphotericin B. However, some species of dematiaceous fungi are resistant to this agent. Once the infection is under control, longer-term therapy with a broad-spectrum oral azole is often reasonable until complete response is achieved, which may require several weeks to months.

Other agents have limited roles in treating these fungi. Ketoconazole is not well tolerated, and fluconazole has poor activity against these fungi in general. Terbinafine and flucytosine have occasionally been used for subcutaneous infections in patients refractory to other therapy. Echinocandins do not appear to be very useful as single agents. Combination therapy is a potentially useful therapeutic strategy for refractory infections, particularly brain abscess and disseminated disease, though it has not been well studied. Suggested therapies for specific infections are summarized in Table 12.1.

Superficial Infections

Itraconazole and terbinafine are the most commonly used systemic agents for onychomycosis, and may be combined with topical therapy for refractory cases [43]. There is no published experience with voriconazole.

Subcutaneous lesions will often respond to surgical excision alone [44]. Oral systemic therapy with a broad-spectrum azole antifungal agent in conjunction with surgery is frequently employed and has been used successfully, particularly in immunocompromised patients [45, 46].

For keratitis, topical 5% natamycin is used almost exclusively, with only a few severe cases requiring adjunctive therapy, usually with an azole [22, 47]. Itraconazole has the best in vitro activity. The majority of isolates are resistant to flucytosine. Surgery, including penetrating keratoplasty, is often needed. Enucleation is occasionally required due to poor clinical response. Many patients do not recover complete visual acuity despite aggressive therapy.

Allergic Disease

Steroids are the mainstay of treatment for allergic disease caused by these fungi, especially in asthma, though other modalities may have a role in specific clinical situations. For example, therapy for AFS consists of systemic corticosteroids and surgery to remove the mucin, which is often tenacious. Antifungal therapy, usually in the form of itraconazole, may play a role in reducing the requirement for corticosteroids, but this is not routinely recommended [48]. Other azoles have only rarely been used for this disease.

ABPM can be treated with systemic corticosteroids as in ABPA; prednisone at a dose of 0.5 mg/kg/day for 2 weeks, followed by a slow taper over 2–3 months or longer [29]. Itraconazole has been used as a steroid sparing agent in APBA, but its efficacy is not clear and routine use of itraconazole is not generally recommended [29].

Pneumonia

Therapy consists of systemic antifungal agents, usually amphotericin B or itraconazole initially, followed by itraconazole for a more prolonged period [16]. Mortality rates are high in immunocompromised patients. Experience with voriconazole is currently only anecdotal [49].

Brain Abscess

Therapy published in the literature has varied greatly depending on the case report, and there is no standard treatment. A retrospective analysis of 101 reported cases suggested that the combination of amphotericin B (high-dose lipid formulation), flucytosine, and itraconazole may be associated with improved survival, though it was not frequently used [35]. Voriconazole may also prove useful. High doses of azoles have been suggested as an option, though there are no studies confirming this approach. Based on animal models and anecdotal reports, some form of combination therapy may be optimal, though specific regimens have not been established [4]. Complete excision of brain abscesses may lead to better outcomes than aspiration or partial excision. Overall mortality is greater than 70 %.

Disseminated Infection

A literature review suggested the mortality rate is greater than 70 %, despite aggressive antifungal therapy [37]. There were no antifungal regimens associated with improved survival in disseminated infection. High-dose lipid amphotericin B may be reasonable for initial therapy, given its fungicidal activity for many fungi. The addition of a broad-spectrum azole or echinocandin could be considered in those failing therapies. Infection with *S. prolificans* has been associated with a nearly 100 % mortality in the absence of recovery from neutropenia, as it is generally resistant to all available antifungal agents. Recent reports have suggested that the combination of itraconazole or voriconazole with terbinafine may be synergistic against this species, though the clinical relevance of this finding is unclear [50, 51].

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