Mucormycosis, Pseudallescheriasis, and Other Uncommon Mold Infections

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Serious infections due to non-*Aspergillus* molds are being encountered with increasing frequency. Factors likely responsible for the rise of these infections include aging populations in countries with advanced medical technologies, the resultant increase in incidence of many cancers, increasingly intensive myeloablative therapies for these cancers, increasingly intensive care for critically ill patients, and increases in the frequency of solid organ and hematopoietic stem cell transplantation. Although diagnostic and therapeutic modalities have improved, mortality rates for invasive mold infections remain high. In this review, we summarize current knowledge about non-*Aspergillus* mold infections of the chest, with a focus on risk factors, clinical features, diagnosis, and treatment.

Keywords: mold infection; mucormycosis; pseudallescheriasis; pneumonia

MUCORMYCOSIS

Mucormycosis is a fungal emergency that virtually always occurs in patients with defects in host defense and/or with increased available serum iron (1). Although mucormycosis is less common than other opportunistic fungal infections, such as those caused by *Candida* and *Aspergillus* spp. (2), the 60% or greater mortality of mucormycosis pneumonia (3–6) is higher than the mortality rates caused by other fungal pathogens.

Microbiology

Mucormycosis is caused by fungi of the order Mucorales. Recent reclassification has abolished the class Zygomycetes and placed the order Mucorales in the subphylum Mucormycotina (7). Therefore, we refer to infection caused by Mucorales as mucormycosis rather than zygomycosis.

Fungi belonging to the order Mucorales are distributed into six families, all of which can cause cutaneous and deep infections (8). Of fungi in the order Mucorales, species belonging to the family Mucoraceae are isolated more frequently from patients with mucormycosis than any other family. Among the Mucoraceae, *Rhizopus* is by far the most common genus causing infection, with *R. oryzae* (*R. arrhizus*) in particular causing 50% or more of mucormycosis cases, and *R. microsporus* causing another 15 to 25% of cases (3, 8, 9). Other, less frequently isolated species of Mucorales cause a spectrum of infections similar to that cause by *Rhizopus* spp. (3, 8, 9).

Clinical Risk Factors

The Mucorales are common environmental fungi, to which humans are constantly exposed. Pulmonary disease is virtually

never seen outside the context of an immunocompromised host, although a handful of case reports over the past half century have described rare occurrences in patients with no known immune deficiency (10).

Pulmonary mucormycosis occurs most commonly in patients with prolonged neutropenia, such as patients with leukemia or those undergoing hematopoietic stem cell transplantation. Indeed, the pulmonary form of mucormycosis is the most common manifestation found in neutropenic or stem cell transplant patients (3, 5). When mucormycosis occurs in the setting of neutropenia, patients typically have severe, prolonged neutropenia and are frequently receiving broad-spectrum antibacterial agents for unremitting fever (11). However, in patients undergoing allogeneic stem cell transplantation, the disease often occurs after resolution of neutropenia after engraftment, and is strongly associated with corticosteroid therapy for graft versus host disease (5, 12).

Diabetes is the most common risk factor overall for mucormycosis, but most diabetics present with rhinoorbital or rhinoorbital-cerebral mucormycosis (3). Diabetes is rarely associated with pulmonary mucormycosis. When pulmonary mucormycosis does occur in patients with diabetes, it may be co-existent with sinus, orbital, or brain disease, and may follow a more indolent, subacute course than is typically seen in patients with neutropenia (11).

Prophylaxis with either itraconazole (13) or voriconazole (14, 15) has been implicated in predisposing to mucormycosis. Posaconazole has *in vitro* activity against the Mucorales (*see below*). However, in its pivotal phase III clinical trials for prophylaxis in patients with prolonged neutropenia, virtually no cases of mucormycosis were seen in either the posaconazole or standard therapy arms (16, 17). Hence, no conclusions can be drawn about its clinical efficacy as a prophylactic agent against mucormycosis.

It is now clearly recognized that patients with elevated available serum iron are at particular risk factor for mucormycosis (1). For example, diabetics in ketoacidosis are uniquely predisposed to mucormycosis. Sera from patients in diabetic ketoacidosis have increased free iron levels compared with control serum due to proton-mediated dissociation of iron from sequestering proteins (18). Furthermore, patients treated with the iron chelator, deferoxamine, also have a markedly increased incidence of invasive mucormycosis. While deferoxamine is an iron chelator from the perspective of the human host, Mucorales actually use deferoxamine as a siderophore to supply previously unavailable iron to the fungus (19). Recognition of the link between iron availability and mucormycosis predisposition has created a novel therapeutic strategy for mucormycosis (*see below*).

Clinical Features

Pulmonary mucormycosis may develop as a result of inhalation or by hematogenous or lymphatic spread. Symptoms of pulmonary mucormycosis include dyspnea, cough, and chest pain (1). In a series of 32 cases of pulmonary mucormycosis, fever was present in the majority of patients (11). Angioinvasion results in necrosis of tissue parenchyma, and may ultimately lead to

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cavitation and/or hemoptysis, which may be fatal if a major blood vessel is involved. A variety of radiographic findings may be present, including lobar consolidation, isolated masses, nodular disease, cavitation, or wedge-shaped infarcts (11, 20). Chest CT scan is the best method of determining the extent of pulmonary mucormycosis. In the setting of cancer, where the diagnosis of invasive mucormycosis may be difficult to differentiate from aspergillosis, multiple pulmonary nodules (i.e., ≥ 10), pleural effusion, or concomitant invasive sinusitis should lead one to favor mucormycosis (21). A recent study reported that the reversed halo sign, a focus of ground glass surrounded by a solid ring of consolidation seen on CT scan, may also be useful in differentiating mucormycosis and aspergillosis (22).

Diagnosis

Establishing the diagnosis of pulmonary mucormycosis is difficult. Because the Mucorales are environmental isolates, which may contaminate laboratory specimens or colonize mucosal surface without causing invasive infection, establishing a definitive diagnosis requires a positive culture from a sterile site (e.g., needle aspirate, tissue biopsy specimen, or pleural fluid) or histopathologic evidence of invasive mucormycosis (23). Probable mucormycosis can be established by culture from a non-sterile site (e.g., sputum or bronchoalveolar lavage) in a patient with appropriate risk factors and clinical and radiographic evidence of disease. Clinical factors predisposing to mucormycosis in this context include diabetes, corticosteroid use, neutropenia, or solid organ or hematopoietic stem cell transplantation. In a patient with such risk factors, with radiographic evidence of pneumonia, a positive culture of Mucorales from a bronchoscopic specimen would indicate a very high degree of suspicion for infection.

Biopsy with histopathologic assessment remains the most sensitive and specific modality to definitively establish a diagnosis of pulmonary mucormycosis. However, patients with pulmonary mucormycosis often have contraindications to invasive biopsies, such as coagulopathies or marked thrombocytopenia. In such patients, bronchoalveolar lavage may be critical to establish the diagnosis. Unfortunately, sputum or bronchoscopic cultures are insensitive for the diagnosis (11). In addition, the organism is killed during tissue grinding (24, 25), which is routinely used to process tissue specimens for culture. As a result, cultures are negative in half or more of cases of mucormycosis. When processing tissue for culture, the microbiology laboratory should be advised that a diagnosis of mucormycosis is suspected, and the tissue should be cut into sections that are placed in the center of culture dishes, rather than being homogenized. Extensive work is ongoing to develop a PCR based test, which may improve the sensitivity and rapidity of diagnosis in the future (26, 27).

Treatment

Four factors are critical for eradicating mucormycosis: rapidity of diagnosis, reversal of the underlying predisposing factors (if possible), appropriate surgical debridement of infected tissue, and appropriate antifungal therapy (1, 28). Early diagnosis is important because small, focal lesions can be surgically excised before they progress to involve critical structures or disseminate. Furthermore, delayed initiation of appropriate antifungal therapy in patients with mucormycosis been associated with increased mortality (29). Correcting or controlling predisposing medical problems is also essential for improving treatment outcome. Specifically, it is critical to maintain tight control of diabetes and to immediately resolve any acidosis. Discontinuation or dose reduction of corticosteroids should be strongly considered when the diagnosis of mucormycosis is made.

Aggressive attempts to restore neutrophil counts, for example by G-CSF administration, should be considered (28).

Blood vessel thrombosis and resulting tissue necrosis during mucormycosis can result in poor penetration of antifungal agents to the site of infection. Therefore, debridement of necrotic tissues may be critical for complete eradication of mucormycosis. In the largest case series of mucormycosis published to date, surgery was an independent variable for favorable outcome in patients with mucormycosis (3), which was concordant with the experience in prior case series (28). Surgical resection and debridement should be strongly considered for pulmonary mucormycosis, if at all possible. Unfortunately, surgical treatment is often not possible in patients with pulmonary mucormycosis, due to thrombocytopenia, coagulopathies, or high operative risk and poor wound healing due to underlying diseases.

Until recently, only members of the polyene class of antifungals, including amphotericin B deoxycholate (AmB) or its lipid derivatives, had been demonstrated to have activity against the agents of mucormycosis. Because the various species that cause mucormycosis have a broad range of susceptibility, high doses of AmB (e.g., 1–1.5 mg/kg/d) have been used to treat mucormycosis, resulting in a very high toxicity rate. The lipid formulations of amphotericin are significantly less nephrotoxic than AmB and can be safely administered at higher doses for a longer period of time. Several case reports and case series of patients with mucormycosis have documented successful outcomes with either liposomal amphotericin B (LAmB) or amphotericin B lipid complex (ABLC) (28). Both ABLC and LAmB penetrate extremely well into the pulmonary parenchyma, achieving levels substantially higher than AmB (30–32). In a recent retrospective review of 120 cases of mucormycosis in patients with hematologic malignancies, treatment with LAmB was associated with a 67% survival rate, compared with 39% survival when patients were treated with AmB ($P = 0.02$, χ^2) (4).

The optimal dosages for treatment of mucormycosis are not known for any antifungal agent (28). Starting dosages of 1 mg/kg/day for AmB and 5–7.5 mg/kg/day for LAmB and ABLC are commonly used in adults and children. Whether higher dosages provide any additional benefit is uncertain, especially for pulmonary disease.

Voriconazole is not active against the Mucorales *in vitro*. Conversely, posaconazole has *in vitro* activity against agents of mucormycosis (33, 34). Unfortunately, serum levels of posaconazole achieved in patients with febrile neutropenia or in those with invasive fungal infections are typically below the MIC₉₀ for the Mucorales (28). Furthermore, as has been recently reviewed (28), data from four groups of investigators indicated that posaconazole was inferior in efficacy to AmB for the treatment of murine mucormycosis, and three groups found that it was not superior to placebo for treating mice infected with *R. oryzae*, the most common cause of mucormycosis.

Based on the available animal data and the absence of clinical data, posaconazole monotherapy cannot be recommended as primary treatment of mucormycosis. In contrast, available clinical data from open-label salvage studies suggest that posaconazole is a reasonable option for patients with mucormycosis who are refractory to or intolerant of polyenes (35, 36).

Combination Antifungal Therapy

Echinocandins have minimal activity against the agents of mucormycosis when tested *in vitro* by standard techniques (37, 38). However, it is now known that *R. oryzae* expresses the target enzyme for caspofungin (25), and in mice with disseminated *R. oryzae* infection, combination of echinocandins (caspofungin, micafungin, or anidulafungin) plus ABLC or LAmB

was synergistic (39, 40). A recent retrospective case series of patients treated for rhinoorbital-cerebral mucormycosis with combination of caspofungin plus ABLC or LAmB showed improved outcomes including long-term survival (41). These data suggest that echinocandins may have a role as a second agent, in combination with a polyene, in serious cases of mucormycosis. More study of the utility of echinocandins in this setting is needed.

Two recent preclinical studies evaluated the efficacy of posaconazole combination therapy for murine mucormycosis. Both studies found that addition of posaconazole to polyenes resulted in no additive benefit compared with polyene therapy alone (42, 43). No clinical studies have evaluated combination posaconazole-polyene therapy for mucormycosis.

As discussed above, the central role of iron metabolism in the pathogenesis of mucormycosis suggests the possibility of using effective iron chelators as adjunctive antifungal therapy. Deferasirox is an orally available iron chelator approved by the United States (U.S.) Food and Drug Administration (FDA) for the treatment of iron overload in transfusion-dependent anemias (44). Deferasirox was fungicidal for clinical isolates of *Mucorales in vitro*, with an MIC₉₀ of 6.25 µg/ml (45). In diabetic mice with disseminated mucormycosis, deferasirox was as effective as LAmB therapy, and combination deferasirox-LAmB therapy synergistically improved survival (80% survival for combination versus 40% for monotherapy versus 0% for placebo) (45). Recent description of open-label deferasirox in eight patients with mucormycosis suggested that the drug was safe in this setting (46). The use of deferasirox as a therapeutic modality in mucormycosis is the subject of an ongoing, double-blinded, placebo-controlled, phase II clinical trial (the DEFEAT Mucor study, NCT00419770).

Only prospective, randomized trials will be capable of determining whether any combination of antifungal agents is more effective than monotherapy for mucormycosis. Until such trials are available, consideration of combination versus monotherapy must be made on a case-by-case basis.

PSEUDALLESCHERIASIS/SCEDOSPORIOSIS

Pseudallescheria boydii (anamorph of *Scedosporium apiospermum*) is a common environmental saprophyte found in nutrient-rich soil and brackish water with a worldwide distribution. *Scedosporium prolificans*, a closely related species, is also a soil saprophyte with a slightly less extensive distribution (47). Entry into the human host is often via traumatic inoculation or through inhalation into the pulmonary system; acquisition can occur in both the community-acquired and nosocomial settings (48). Like mucormycosis, infections due to *P. boydii* and *S. prolificans* are becoming more common in the era of prolonged immunosuppression.

Risk Factors and Clinical Features

Like other mold infections, pseudallescheriasis has been rarely reported in immunocompetent patients (49, 50), and the disease typically occurs in immunocompromised hosts (5, 51, 52). Pseudallescheriasis may cause widespread disseminated infection in patients who have received hematopoietic or solid organ transplants (52–54). Central nervous system disease has been associated with patients suffering from near-drowning episodes (55). Patients with cystic fibrosis and chronic granulomatous disease are also predisposed to developing infection with this fungus (53, 54, 56).

Pulmonary infection is a common manifestation of pseudallescheriasis. Patients can be asymptomatic or they may present with various combinations of fever, cough, night sweats, weight

loss, or chills (52–54). Like *Aspergillus*, *P. boydii* and *S. prolificans* can form fungus balls in patients with pre-existing cavitory lung disease or in patients with severe immunocompromise (57–59). Pulmonary findings may be localized or may be part of more disseminated disease (53). Airway colonization without invasive infection has also been described (47). Symptoms of disease include high fevers, dyspnea, cough, and other nonspecific complaints (60, 61). Radiographic findings of pulmonary pseudallescheriasis are not distinctive compared with those of other mold infections, and can include pulmonary infiltrates, lobar consolidation, mass lesions, nodules with or without cavitation, necrotizing pneumonias, or pulmonary abscesses (49, 50, 56, 61–63).

Diagnosis

As for all mold infections, diagnosis of pseudallescheriasis/scedosporiosis is challenging. Unfortunately the organism cannot be distinguished from other septated molds (such as *Aspergillus*) by histopathology. Blood cultures may be positive during disseminated pseudallescheriasis and scedosporiosis (63). Ultimately, confirmation of diagnosis depends on the isolation of the organism in culture.

Treatment

P. boydii is susceptible to the triazoles voriconazole and posaconazole *in vitro*, and is somewhat less susceptible to AmB (64). Voriconazole is approved by the U.S. FDA for the treatment of *P. boydii* infections refractory to other antifungals. In one large series, treatment with voriconazole was associated with a strong trend to superior survival compared with treatment with AmB (65).

In contrast to *P. boydii*, *S. prolificans* tends to be highly resistant to azoles, and indeed most other antifungal options (66). Addition of terbinafine or other antifungal agents to voriconazole as part of a combination therapy regimen may be considered when treating infection caused by *S. prolificans*, but robust data are lacking on the relative efficacy of combination therapy versus voriconazole monotherapy. Surgical resection is critical for treatment of patients infected with *S. prolificans*, since the organism is often resistant to antifungal therapy, and mortality from disseminated infection caused by *S. prolificans* approaches 90 to 100% (52, 53).

FUSARIOSIS

Increases in transplantation and use of immune-suppressing agents have led to a rise in incidence of nosocomial *Fusarium* infections (67, 68). The rise in fusariosis incidence may also be partially attributable to the routine use of fluconazole prophylaxis after transplant (5). Colonized water systems in the hospital environment have been identified as reservoirs of *Fusarium*, and aerosolization and patient-to-patient spread subsequently may lead to infections (69).

Risk Factors and Clinical Features

Fusariosis may occur in immunocompetent hosts manifesting as soft tissue or mucosal infections after direct inoculation of the mold into the skin or eye (i.e., keratitis due to contact lenses) by trauma, foreign body, or burns (68). In contrast, invasive fusariosis is essentially a nosocomial disease of the immunocompromised. The severity and duration of immune suppression appear to be the most important factors in creating risk for fusariosis, and patients undergoing hematopoietic stem cell transplantation are at highest risk (67, 68). As with other invasive molds, neutropenia is the major risk factor for development of early disease (within 30 d of transplant), while

later presentation (>30 d) occurs in the setting of corticosteroid therapy for graft-versus-host disease (67, 68). By contrast, fusariosis is rare among solid-organ transplant patients, and has a much lower mortality rate in this population (70). Fusariosis has also been described in the setting of chronic granulomatous disease (71) and in immunocompromised patients with indwelling catheters (72).

Although it has been described in an immunocompetent host (73), pulmonary fusariosis is far more common in immunocompromised patients, usually in association with disseminated infection (68). Disseminated infections typically present with skin lesions, most commonly with purpuric nodules with central necrosis (68, 74). In one series, 75% of fusariosis cases presented with skin lesions in the setting of disseminated infection (67). In a recent study of 20 patients with hematologic malignancies and known or suspected fusariosis, chest radiographs were negative in 25% of patients that had abnormal chest CTs (75). The predominant findings on chest CT (82% of cases) were nodules or masses, although consolidation was also identified in some patients.

Diagnosis

Biopsy of skin lesions during disseminated fusariosis typically reveals histopathologic evidence of vascular invasion (67). On histopathologic examination, the organism appears as hyaline, acute-branching, septate hyphae that may be indistinguishable from *Aspergillus* species. Unlike many other invasive molds, *Fusarium* frequently grows from blood cultures (i.e., >40–75% of cases) (68, 74).

Treatment

Fusarium spp. tend to be less susceptible to polyenes *in vitro* than other molds, and breakthrough infections have occurred on polyene therapy (76). The most effective therapy for fusariosis has not been defined. Successful outcomes have occurred with voriconazole or with AmB or its lipid formulations (68). Posaconazole salvage therapy may be useful for refractory disease (77). Various combination regimens, including echinocandin-polyene, azole-polyene, and polyenes or azoles plus terbinafine, have been described in case reports (68). Whether or not combination therapy is more effective than monotherapy has not been determined (68).

Reversal of the underlying immune suppression is crucial in the therapeutic approach to fusariosis. Specifically, a reduction of duration of neutropenia by administration of colony-stimulating factors, or, possibly by white cell transfusions, may be attempted. Background corticosteroid therapy should be reduced or eliminated, if feasible.

OTHER MOLDS

A variety of other molds have been implicated in nosocomial infections, including *Acremonium*, *Paecilomyces*, *Cladophiala*, *Cladosporium*, and many other hyalohyphomycetes and dematiaceous fungi. These infections occur in similar patient populations and can be diagnosed and treated in a similar fashion to pseudallescheriasis. In general, susceptibility testing of cultured molds can be very helpful to guide long-term therapy.

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