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FUNGAL INFECTIONS IN TRANSPLANTATION (S SHOHAM, SECTION EDITOR)

Mucormycosis in Solid Organ Transplant

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Abstract

Purpose of review Although mucormycosis remains an uncommon opportunistic fungal infection, new advances in diagnostic testing and in treatment have evolved to manage patients with such infections. The goal of this review is to determine how such advances have affected the management of mucormycosis.

Recent Findings Fungal prophylaxis with voriconazole or caspofungin may increase the risk of mucormycosis in transplant recipients. Imaging the affected organ systems permits the extent of disease to be delineated and can inform decisions on surgical therapy. First-line treatment includes high-dose liposomal amphotericin B; intravenous isavuconazole and intravenous or delayed-release tablet posaconazole are alternatives and are also options for salvage therapy. Combination therapy has not proven to be more effective than monotherapy.

Summary Optimal management of mucormycosis depends on early recognition of the disease patterns and on confirmation with culture when possible. Biomarkers of fungal for diagnosis and management are not specific enough and more research in this area might permit pre-emptive therapy when applied to high-risk recipients. Effective therapy is generally a combination of surgery with an antifungal agent.

Keywords Mucormycosis · Zygomycosis · Mold infection · Rhizopus

Introduction

Mucormycosis is an invasive fungal infection caused by species within the *Mucorales* order. Genera include *Rhizopus*, *Mucor, Lichthemia*, *Syncephalastrum*, *Saksenaea*, *Cunninghamella*, *Rhizomucor*, and *Apophysomyces*. While rare, it can be an aggressive angioinvasive infection in solid organ transplant (SOT) recipients [1••, 2•]. *Mucorales* species are the second commonest pathogens in SOT patients, after *Aspergillus* [2•]. The majority of patients with mucormycosis are male, older than 40 years of age, and have risks factors including poorly controlled diabetes mellitus, renal failure, prolonged neutropenia, active malignancy, iron overload, high-dose corticosteroids, and immunosuppressive therapy [1••, 2•, 3, 4••]. In low and middle-income countries, diabetes mellitus is the main risk factor. Since the incidence of diabetes is rising there, an alarming rise in mucormycosis cases is projected. However, in developed countries, hematological malignancies and transplantation are the most common underlying diseases [4••].

Advances in immunomodulating agents used in the treatment of cancer and autoimmune diseases are affecting the epidemiology of mucormycosis [4••]. While mucormycosis remains an uncommon complication of SOT (incidence of 0.007% at 1 year after transplantation), overall mortality can exceed 80% [2•, 3]. As expected for a predominantly respiratory infection, incidence is related to the organ being transplanted; the highest incidence is in lung transplant recipients and the lowest in renal transplant recipients. Interestingly, however, one single-center study demonstrated that renal recipients had the highest number of cases, likely due to the discrepancy in the total number of transplants done comparing renal to lung recipients [5]. Most infections occur within 6 months of solid organ transplant, especially in liver transplant recipients [1••]. The southern USA has the highest

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incidence of mucormycosis compared to other regions of the country [3].

Geographically, the prevalence of mucormycosis in India is about 80 times the prevalence in developed countries, being approximately 0.14 cases per 1000 population [4••]. This may be due to the predilection for these spores of these species to be found in nature in natural composts and tropical soils [1••]. Mucormycosis in renal transplant recipients is more common in India than it is in developed countries. SOT is a risk factor in 2.6–11% of mucormycosis cases from India. The prevalence of mucormycosis in renal transplant recipients in India varies from 0.05 to 2.7%, compared to global data of 0.04–0.05% [6]. This higher prevalence in India may have several causes including abundant presence of *Mucorales* in the community, large number of pts with diabetes mellitus, and the neglect for regular health checkups in parts of the Indian population. Other predisposing factors associated with mucormycosis in India are chronic kidney disease, pulmonary tuberculosis, and corticosteroid therapy [6].

Chronic administration of corticosteroids and other immunosuppressive agents are important risk factors for mucormycosis. Corticosteroids impair migration, ingestion, and phagolysosome fusion in macrophages. High-dose systemic corticosteroids administered for at least 3 weeks may lead to drug-induced hyperglycemia [4••]. Concomitant or recent voriconazole or casponfungin use also seem to increase the risk of mucormycosis [1••, 7]. This is perhaps due to these antifungal agents not having activity against mucormycosis]. Paradoxically, tacrolimus, a calcineurin-inhibitor, appears to decrease risk for mucormycosis [4••]. Recent analysis of the calcineurin pathway in *Mucor* spp. has revealed that calcineurin, a serine-threonine phosphatase, regulates yeast-mycelium transition and virulence. The addition of calcineurin inhibitors result in a less virulent form of *Mucor* spp. That is locked in the yeast phase. These studies suggest a link between dimorphism and virulence and may offer a promising target for antifungals directed to mucormycosis [8].

Rapid diagnosis of mucormycosis remains challenging as no pathognomonic serological or antigenic markers exist. Clinical presentation is highly heterogeneous, and it can involve a specific organ or be disseminated [1••, 9]. Prolonged fever unresponsive to broad-spectrum antibiotics is usually present as well as nonproductive cough for those with pulmonary involvement [4••]. The detection of both galactomannan antigen and 1–3-β-D glucan is less valuable for diagnosis because of *Mucorales* [7]. The histopathgoical hallmark is tissue necrosis resulting from angiocentric invasion leading to thrombosis [1••]. Angioinvasion leads to hematogenous dissemination, whereas necrosis of the affected tissues prevents penetration of immune cells and antifungal agents to the site of infection focus [10]. Mucormycosis may also cause necrotic skin lesions. However, the differential diagnosis remains broad for this finding, including other opportunistic pathogens such as *Pseudomonas* (ecythema gangrenosusm), *Aspergillus*, *Fusarium*, *Pseudallescheria*, and *Scedosporium* species.

Rhino-oribtal-cerebral, pulmonary, gastrointestinal, and disseminated disease are the most common types of infection [3]. Rhino-orbital-cerebral mucormycosis is the most common form of the disease in India, followed by the pulmonary and the cutaneous types. However, the pulmonary form is the most common clinical presentation in developed countries. The cutaneous type is commonly seen in patients with trauma or burns [6]. Pulmonary mucormycosis is the most common site of infection for renal transplant patients [3]. In all of these circumstances, diagnosis on clinical features alone is challenging. Additionally, in countries where tuberculosis is endemic, the two infections may coexists [4••].

The differential diagnosis of fungal infections in immunocompromised patients includes invasive aspergillosis and other mold infections. Most mold infections can occur as slowly or non-resolving pneumonias or as invasive extrapulmonary infections, particularly of the skin and soft tissue and rhino-sinusal regions or other areas [2•, 7]. Various radiologic findings have been studied to help differentiate between the two. Recent studies of pulmonary mucormycosis suggests that early imaging includes peribronchial ground-glass opacities while later in the disease, imaging will show consolidation, nodules, or masses [11]. Other radiologic findings include the reverse halo sign, an area of ground-glass opacity surrounded by a rim of consolidation, as well as the presence of pleural effusions and more than 10 nodules [11].

Definitive diagnosis of mucormycosis is based on the demonstration of non-pigmented, wide (5–20 μm), thin-walled, ribbon-like hyphae with no or few septations and right-angle branching in biopsies of affected tissues [4••]. In respiratory infections, invasive procedures such as open pulmonary resection, transthoracic CT-guided biopsy and, in the case of rhino-cerebral forms, by samples obtained through nasal endoscopy [7]. Newer molecular diagnostic techniques, such as in situ hybridization and PCR, offer an alternative which may lead to earlier diagnosis and prompt initiation of treatment [1••].

Any attempt at successful management of mucormycosis will require a multi-disciplinary approach. This will modifying predisposing factors, early administration of active antifungal agents, and complete removal of all infected tissues [1••, 10]. Immunosuppressive drugs should be tapered to the lowest possible dose, preferably quickly. Promptly initiating therapeutic interventions is necessary for preventing progressive tissue invasion and necrosis, and improving outcome and survival [10]. Muccor isolates generally

susceptible to amphotericin B, posaconazole, and isavuconazole, but not to fluconazole, voriconazole, or echinocandins [7]. Lipid formulations of amphotericin B currently are the backbone of antifungal treatment for mucormycosis. Posaconazole is considered a second-line drug and is recommended for salvage therapy [7].

Isavuconazole is a newer azole option to treat mucormycosis. It lacks the nephrotoxicity associated with liposomal amphotericin B. Isavuconazole also has displays minimal interaction with calcineurin inhibitors. Although isavuconazole is an inhibitor of cytochrome P450, it inhibits only one isoenzyme compared while voriconazole inhibits three. Isavuconazole was approved as an alternative first-line treatment of mucormycosis, but many continue to recommend liposomal amphotericin B remains the drug-of-choice pending further study and real world experience. The expanded role of isavuconazole in prophylaxis and treatment of fungal infections in SOT patients begs further study [12]. The duration of treatment with antifungal agents is not known. Active agents that have oral formulations such as posaconazole and isavuconazole are preferred because they can be administered for several months, if needed [10].

Surgery is an important element in managing mucormycosis, particularly for rhino-orbital-cerebral forms and for mucormycosis of skin and soft tissues [7]. Necrotic tissue with a rim of surrounding infected healthy-looking tissues should be removed quickly given the rapid progression of infection by *Mucorales* hyphae [10]. Due to the aggressive spread of mucormycosis in SOT patients, extensive surgical debridement appears to be necessary in successful clearance of disease. Surgical debridement of infected tissues has been associated with an improved survival when combined with medical treatment. In SOT recipients, surgery is associated with increased survival rates especially for pulmonary and rhino-orbital-cerebral mucormycosis [9]. Repeated surgical intervention may be necessary to achieve surgical control. In cases with a successful outcome, plastic surgery may be necessary to correct disfigured body areas [10].

Conclusion

Mucormycosis, an infection that can be caused by members of several genera of molds, is a rare complication of SOT but one often associated with significant mortality and morbidity. The organisms are ubiquitous and tend to be acquired through the respiratory tract. Progression of disease can be rapid, and diagnosis requires a high level of suspicion and prompt tissue biopsy with appropriate stains. Optimal management of mucormycosis includes early recognition of the disease patterns, confirmation with culture when possible, and effective therapy with a combination of liposomal amphotericin and surgery. Newer oral agents may prove to be useful and cost-effective options once control of infection has been achieved.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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