Emergence of the Molds Other than *Aspergillus* in Immunocompromised Patients

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KEYWORDS

• Mucormycosis • *Fusarium* • *Scedosporium* • Immunocompromised • Transplant
• Dematiaceous mold • *Lomentospora prolificans*

KEY POINTS

- Clinical and radiographic presentations of sinopulmonary mold infections tend to be similar; culture and histopathology are needed to make a diagnosis.
- Mucorales infections tend to most commonly involve the lungs and sinuses. Skin involvement is usually due to trauma and is rarely seen in disseminated infection.
- Blood cultures in *Aspergillus* and Mucorales infections are usually negative. *Fusarium* and *Scedosporium* frequently yield positive blood cultures in disseminated infections.
- Although susceptibility testing can be done on emerging fungal pathogens, such as Mucorales, dematiaceous molds and *Fusarium*, no standardized break points are available as of yet.
- The management of most mold infections tends to be complex and requires a combination of surgical debridement, antifungal therapy, and possibly adjunctive therapy.

As medical science advances, more patients are becoming eligible for solid organ transplants (SOTs) and stem cell transplants (SCTs), hence, increasing the population of severely immunocompromised patients. The lack of an adequate immune system has made these patients more prone to infections from organisms that were previously considered environmental contaminants and not true pathogens. A major fraction of these pathogens are fungi such as Mucorales, dematiaceous molds, and plant pathogens such as *Fusarium*. These emerging fungi are associated with high mortality, and our understanding in regard to their pathogenesis and treatment is limited.

MUCORALES

Over the years there have been significant changes to the nomenclature used for this group of fungi. After the establishment of the fungal kingdom (1968), they were initially classified in the phylum Zygomycota. The phylum contained 10 different orders, including Mucorales and Entomophthorales. Infections due to organisms belonging to these two orders were referred to as zygomycosis.[1]

In the 1990s, when taxonomists started to apply molecular techniques, to obtain a better understanding of fungal lineages, it was noted that the Zygomycota were actually polyphyletic. In 2007 Hibbett and colleagues[2] suggested eliminating Zygomycota as a phylum and raising 4 of its orders, including Mucorales and Entomophthorales, to the rank of subphyla. This action led to the reuse of the term *mucormycosis*.[3] Although the term sounds like it would mean infections due to the *Mucor* species, it reflects infection due to all fungi in the Mucorales order. In recent years, the terms *zygomycosis* and *mucormycosis* have

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been used somewhat interchangeably from a clinical standpoint. However, in this discussion the authors use the most recent designation of mucormycosis.

Epidemiology

The epidemiology of mucormycosis is very complex and not well understood. As Mucorales are a common part of the general environment, there can be differences in exposure, based on geographic location and seasonality.[4] A significant volume of the literature has focused on the development of mucormycosis in diabetic patients, and data on immunocompromised hosts are relatively limited but starting to increase.

A review of 929 cases of mucormycosis revealed that diabetes was the most commonly associated risk factor, affecting 36% of the reported cases.[5] In countries such as India, diabetes continues to remain the most common risk factor.[6,7] However, in more developed countries, the infection is encountered more frequently in patients with hematologic malignancies. A retrospective study from France identified 101 cases of mucormycosis, between 2003 and 2007, from the French hospital information system. It showed that the most common underlying condition was hematologic malignancies (50%), followed by diabetes (23%). Fifty-eight percent of the patients were men, and the mean patient age was 50.7 years. The median time from diagnosis of malignancy to the development of infection was 8.8 months. Twelve patients had received a hematopoietic SCT (HSCT), and the median time between HSCT and development of mucormycosis was 6.8 months.[8]

The Transplant Associated Infections Surveillance Network (TRANSNET) is a network of 24 transplant centers across the United States that collected data on invasive fungal infections (IFIs) in transplant recipients (SOT and HSCT) between 2001 and 2006. Eight percent of the cases in HSCT recipients were due to mucormycosis, with a 12-month cumulative incidence of 0.29%. The median time of onset of infection after transplantation was 135 days.[9] Among SOT recipients, the 12-month cumulative incidence was much lower at 0.07%. The highest incidence was seen in lung transplant (0.18%) and liver transplant (0.16%) recipients. Approximately 38% of the infections occurred within the first 6 months following transplantation. It was observed that the median time to infection after transplant was significantly shorter in liver transplant recipients (81 days), when compared with nonliver SOT recipients (533 days).[10]

There is concern that many studies might underestimate the true incidence of these infections as most studies only include patients with proven or probable infection, hence, missing many patients who do not meet the European Organization for Research and Treatment of Cancer/Mycoses Study Group's criteria.[10,11] At this time it is difficult to obtain robust histopathological confirmation of disease from many studies. However, it is largely thought that the number of cases have increased recently, though most of this is based on data from single centers.[12–14] The reasons for an increase in mucormycosis cases are unclear. It is likely multifactorial, including changes in immune suppressive regimens, stem cell sources, antimicrobial prophylaxis practices, and the ability to prolong life with aggressive chemotherapy and other adjunctive therapies.

Pathogenesis

The primary mode of acquiring mucormycosis is by inhalation of spores. The spores are typically 3 to 11 μm in size.[4] Hence, they can reach the alveolar spaces of the lung. Larger spores may get trapped in the nasal or sinus passages, leading to sinusitis. After inhalation, the spores tend to germinate into hyphae. Mononuclear and polymorphonuclear phagocytic cells are key in prevention of fungal proliferation at this stage. Factors such as corticosteroid use and uncontrolled diabetes can cause defective chemotaxis, impair phagocytosis, and impair the cell's intracellular killing mechanisms.[15]

The presence of burns or trauma can result in direct inoculation of the organism into the wound. Outbreaks have been dramatically associated with natural disasters, such as the tornado in Joplin, Missouri in 2011 and the Indian Ocean tsunami of 2004. It is also associated with the classic road rash resulting from motor cycle injuries. Health care–associated outbreaks have been linked to contaminated equipment, such as surgical dressings and tongue depressors, and from direct inoculation into tissue.[16]

The virulence factors of the various Mucorales species are not well understood. The fungus tends to attach to the extracellular protein matrix surrounding blood vessels. It is characterized as a vasotropic fungus. Animal model data suggest that the GRP78 receptor on the surface of endothelial cells facilitates invasion and damage of the cells by the mold.[17] The hyphae, thus, tend to be angioinvasive and cause significant tissue necrosis and thrombosis of vessels. This further impairs the ability of host immune mechanisms and antifungal agents to reach the site of infection, allowing the spread of infection.