242 Mucormycosis

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Mucormycosis represents a group of life-threatening infections caused by fungi of the order Mucorales of the subphylum Mucoromycotina (formerly known as the class Zygomycetes). Infection caused by the Mucorales is most accurately referred to as *mucormycosis*, although the term *zygomycosis* may still be used by some sources. Mucormycosis is highly invasive and relentlessly progressive, resulting in higher rates of morbidity and mortality than many other infections. However, recent studies have suggested that mortality rates from mucormycosis have declined with newer therapies. A high index of suspicion is critical for diagnosis, and early initiation of therapy—often before confirmation of the diagnosis—is necessary to optimize outcomes.

ETIOLOGY

Fungi of the order Mucorales belong to seven medically relevant families (Table 242-1), all of which can cause mucormycosis. Among the Mucorales, *Rhizopus oryzae* (in the family Mucoraceae) is by far the most common cause of infection in the Western Hemisphere. Less frequently isolated species of the Mucoraceae that cause a similar spectrum of infections include *Rhizopus microsporus*, *Rhizomucor pusillus*, *Lichtheimia corymbifera* (formerly *Absidia corymbifera*), *Apophysomyces elegans*, and *Mucor* species (which, despite its name, only rarely causes mucormycosis). Increasing numbers of cases of mucormycosis due to infection with *Cunninghamella* species (family Cunninghamellaceae) have also been reported, particularly in highly immunocompromised patients. Rare case reports have demonstrated the ability of fungi in the remaining families of the Mucorales to cause mucormycosis, although other Mucorales can be the major cause of disease in certain geographic areas (e.g., *A. elegans* in India and *Mucor irregularis* in China).

PATHOGENESIS

The Mucorales are ubiquitous environmental fungi to which humans are constantly exposed. These fungi cause infection primarily in patients with diabetes or defects in phagocytic function (e.g., those associated with neutropenia or glucocorticoid treatment). Patients with elevated levels of free iron, which supports fungal growth in serum and tissues, are likewise at increased risk for mucormycosis. In iron-overloaded patients with end-stage renal failure, treatment with deferoxamine predisposes to the development of rapidly fatal disseminated mucormycosis; this agent, an iron chelator for the human host, serves as a fungal siderophore, directly delivering iron to the Mucorales. Furthermore, patients with diabetic ketoacidosis (DKA) are at high risk of developing rhinocerebral mucormycosis. The acidosis causes dissociation of iron from sequestering proteins in serum, resulting in enhanced fungal survival and virulence. Nevertheless, the majority of diabetic patients who present with mucormycosis are not acidotic, and, even absent acidosis, hyperglycemia directly contributes to the risk of mucormycosis by at least three likely mechanisms: (1) hyperglycation of iron-sequestering proteins, disrupting normal iron sequestration; (2) upregulation of a mammalian cell receptor (GRP78) that binds to Mucorales, enabling tissue penetration (due to both a direct effect of hyperglycemia and increasing levels of free iron, which independently enhances GRP78 expression); and (3) induction of poorly characterized defects in phagocytic function.

TABLE 242-1 TAXONOMY OF FUNGI CAUSING MUCORMYCOSIS (SUBPHYLUM MUCOROMYCOTINA, ORDER MUCORALES)

Family	Genus (Species Listed for Some)
Mucoraceae	*Rhizopus oryzae*
	Rhizopus microsporus
	Rhizomucor
	Mucor
	Actinomucor
Lichtheimiaceae	*Lichtheimia* (formerly *Mycocladus*, formerly *Absidia*)
Cunninghamellaceae	*Cunninghamella*
Thamnidiaceae	*Cokeromyces*
Mortierellaceae	*Mortierella*
Saksenaceae	*Saksenaea*
	Apophysomyces
Syncephalastraceae	*Syncephalastrum*

EPIDEMIOLOGY

Mucormycosis typically occurs in patients with diabetes mellitus, solid organ or hematopoietic stem cell transplantation (HSCT), prolonged neutropenia, or malignancy. The majority of diabetic patients are not acidotic on presentation with mucormycosis. Furthermore, patients often have no previously recognized history of diabetes mellitus when they present with mucormycosis. In these instances, presentation for mucormycosis may result in the first clinical recognition of hyperglycemia, which may have been unmasked by recent glucocorticoid use. Thus a high index of suspicion of mucormycosis must be maintained, even in the absence of a known history of diabetes, if hyperglycemia is present. In patients undergoing HSCT, mucormycosis develops at least as commonly during nonneutropenic as during neutropenic periods, probably because of glucocorticoid treatment of graft-versus-host disease. Mucormycosis can occur as isolated cutaneous or subcutaneous infection in immunologically normal individuals after traumatic implantation of soil or vegetation (e.g., due to natural disasters or motor vehicle accidents) or in nosocomial settings via direct access through IV catheters, SC injections, or maceration of the skin by a moist dressing.

Patients receiving antifungal prophylaxis with either itraconazole or voriconazole may be at increased risk of mucormycosis. These patients typically present with disseminated mucormycosis, the most lethal form of disease. Breakthrough mucormycosis also has been described in patients receiving posaconazole or echinocandin prophylaxis.

CLINICAL MANIFESTATIONS

Mucormycosis can be divided into at least six clinical categories based on clinical presentation and the involvement of a particular anatomic site: rhino-orbital-cerebral, pulmonary, cutaneous, gastrointestinal, disseminated, and miscellaneous. These categories of invasive mucormycosis tend to affect patients with specific defects in host defense. For example, patients with DKA typically develop the rhino-orbital-cerebral form and much more rarely develop pulmonary or disseminated disease. In contrast, pulmonary mucormycosis occurs most commonly in leukemic patients who are receiving chemotherapy and in patients undergoing HSCT.

Rhino-Orbital-Cerebral Disease Rhino-orbital-cerebral mucormycosis continues to be the most common form of the disease. Most cases occur in patients with diabetes, although such cases (probably due to glucocorticoid use) are increasingly being described in the transplantation setting, often along with glucocorticoid-induced diabetes mellitus. The initial symptoms of rhino-orbital-cerebral mucormycosis are nonspecific and include eye or facial pain and facial numbness followed by the onset of conjunctival suffusion and blurry vision. Fever may be absent in up to half of cases. White blood cell counts are typically elevated as long as the patient has functioning bone marrow. If untreated, infection usually spreads from the ethmoid sinus to the orbit, resulting in compromise of extraocular muscle function and proptosis, typically with chemosis. Onset of signs and symptoms in the contralateral eye, with resulting bilateral proptosis, chemosis, vision loss, and ophthalmoplegia, is ominous, suggesting the development of cavernous sinus thrombosis.

Upon visual inspection, infected tissue may appear to be normal during the earliest stages of fungal spread, then progressing through an erythematous phase, with or without edema, before the onset of a violaceous appearance and finally the development of a black necrotic eschar. Infection can sometimes extend from the sinuses into the