An Overview of Mucormycosis

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Mucormycosis is a systemic fungal infection caused by members of the order Mucorales that occurs in patients debilitated by immune or metabolic disorders.

Predisposing conditions and forms of the disease are reviewed.

Diagnosis from direct examination and histological sections of clinical material is reviewed.

Culture requirements, fungal structures of the Mucorales, and microscopic morphology of the 5 genera responsible for infection are reviewed.

Treatment and prognosis of the disease are reviewed.

Mucormycosis is a systemic fungal infection caused by members of the class Zygomycetes, order Mucorales. It is seen in patients debilitated by immune or metabolic disorders.1-5 The class Zygomycetes consists of septate hyaline molds that reproduce by sexual and asexual means. These fungi are ubiquitous in soil and decaying vegetation. Five genera in the order Mucorales are responsible for disease in humans: Rhizopus, Mucor, Absidia, and rarely, Saksenaea and Cunninghamella.1-5

Patients contracting this infection uniformly suffer from predisposing conditions: acidosis, uncontrolled diabetes mellitus, leukemia, lymphoma, AIDS, severe malnourishment, severe burns, cytotoxic therapy, and immune suppression from corticosteroid use.1,2,4-8 It has also been observed in patients with chronic renal failure, liver problems, and dialysis patients on deferoxamine therapy.6,8

There are no known predispositions based on age, race, or sex.8 Most cases are acute surgical emergencies, though a few chronic, indolent forms have been reported with signs and symptoms developing over a 4-week period.8 The primary sites of invasion are the paranasal sinuses, lungs, skin, and the GI tract.1-4,8

Clinical symptoms, signs, and pathological findings are similar in mucormycosis, regardless of etiology.1 These fungi show a predilection for arterial invasion, causing extensive emboli and necrosis of surrounding tissues.2,3,7 Vein and lymphatic invasion can occur later in the course of the infection.3 The acidotic, hyperglycemic environment existing in patients with ketoacidotic diabetes mellitus particularly favors the growth of Rhizopus.1,8 It is thought that diabetic and immunocompromised patients lack normal phagocytic activity on their nasal and oral mucosal surfaces. This allows proliferation of fungus, which does not occur in people with intact phagocytic activity, and the fungus spreads via the blood vessels.8

There are 5 forms of the disease:

- **Rhinocerebral.** This is the most common form, usually seen in patients with ketoacidotic diabetes mellitus.1,2,7 This form presents with sinusitis, facial and eye pain, proptosis, progressing to signs of orbital structure involvement.2,4,7 Necrotic tissue can be seen on the nasal turbinates, septum, and palate. This may look like a black eschar.1,8 Intracranial involvement develops as the fungus progresses through either the ophthalmic artery, the superior fissure, or the cribiform plate.2,6,8

- **Pulmonary.** This is most frequently seen in patients with neutropenia, such as those with leukemia or lymphoma.2,4,7 This form presents with fever, dyspnea, and possible hemoptysis.5,7

- **GI tract.** This form is seen in severely malnourished patients, particularly in kwashiorkor, and has been seen in patients with amoebic colitis and typhoid.1,2,4,7 The stomach, ileum, and colon are usually involved, mimicking intra-abdominal abscess.2,6,7

- **Cutaneous.** This form can follow minor trauma, insect bites, wounds, burns, and use of non-sterile dressings.1,2,4,6,7 Necrotic lesions occur on the epidermis that are painful and hardened, usually with a blackened central area.5,7 These lesions can progress into the dermis and even muscle.7

- **Disseminated.** Dissemination can occur, mainly from the pulmonary form, to the heart, brain, bones, kidney, and bladder.2,4 Dialysis patients on deferoxamine therapy are predisposed to this form.4

**Diagnosis**

Rapid diagnosis and initiation of therapy is critical due to the acute, fulminate nature of the infection.1,6-8 Diagnosis of mucormycosis rests upon the presence of predisposing conditions, signs and symptoms of disease, observation of fungal elements of specific morphology in histological sections, and direct smears of material, and, to a lesser extent, culture re-
There are no reliable serological methods for diagnosis at present. Direct examination in 10% KOH of scrapings from the upper turbinates, aspirated sinus material, sputum, and biopsy material can be valuable. The presence of thick-walled, aseptate, and refractile hyphae 6 to 15 µm in diameter, with some hyphae being swollen and distorted, is indicative of the presence of Mucorales fungi.

Histological sections show acute suppurative inflammation with focal areas of granulomatous inflammation. There are aseptate hyphae 6 to 50 µm in diameter, branching at 90°. The hyphae invade the adjacent blood vessel walls, producing thrombosis and infarction, but rarely disseminate through the vessels. Staining with Grocott-Gomori methenamine silver is best, though periodic acid-Schiff and hematoxylin & eosin (H&E) stains can be used. Diagnosis is frequently made from tissue sections.

Differentiation from *Aspergillus* and *Candida* must be made on histological section. *Aspergillus* and *Candida* do not take H&E stain. *Aspergillus* has septate, narrow, acutely branching hyphae with smooth, parallel walls. *Candida* has septate, narrow hyphae in tissue, with club-shaped pseudohyphae and yeast forms present.

A culture result, by itself, is not diagnostic of infection, since Mucorales fungi are common in the environment. Culture is ideally done on biopsy specimens. Exudates and necrotic tissue contain few viable organisms; thus the inoculum from these specimens must be heavy. Zygomycetes do not survive for more than a few hours at refrigerator temperatures, so if culture is delayed, storage in Stuart’s bacteriological transport media at room temperature is recommended. Sabouraud’s dextrose agar or brain-heart infusion agar are most commonly used for isolation. Media containing cycloheximide must be avoided, as it inhibits the Zygomycetes. Antibacterial agents, such as chloramphenicol and polymyxin B, can be used to prevent bacterial overgrowth. Cultures should be set at 25°C and 37°C aerobically and incubated for 2 to 5 days. Other media good for inducing sporulation necessary for species are potato dextrose malt agar, Czapek solution agar, and hay infusion agar.

Colonies produce fluffy white, gray, or brown hyphae filling the culture container within 24 to 96 hours. The hyphae are coarse and dotted with brown or black sporangia. It is impossible to distinguish the genera based on colony morphology, as they appear similar.

Identification of genera is based on the presence of aseptate hyphae, the structure of the sporangiophore, and the presence and position of rhizoids relative to the sporangiophores. Lactophenol cotton blue can be used to better visualize...
microscopic structures. Identification to the genus level is not very difficult and can be of great value to the physician in a critical situation. Speciation is difficult and is best left to a reference laboratory experienced in fungal identification. See F1 for structures.

Rhizopus sp. are the most often recovered organisms from specimens. They exhibit unbranched sporangiophores that occur singly or in groups at nodes, directly above the rhizoids. The nodes are connected by stolons. The sporangia are dark walled and spherical. Species predominantly recovered are R. oryzae and R. arrhizus.1,2,5,7,9

Mucor sp. are the next most recovered organism from specimens. This genus demonstrates aerial unbranched and branched sporangiophores arising randomly from mycelia. No rhizoids are present. The sporangia are large and spherical. The main species recovered are M. circinelloides, M. ramosissimus, and M. javanicus.1,2,5,7,9

Absidia sp. demonstrates branching sporangiophores arising from nodes between rhizoids. The sporangia are pyriform. Species predominantly recovered are A. ramose and A. corymbifera.1,2,5,7,9

Cuminghamella bertholletiae and Saksenaea vasiformis have been isolated on rare occasions from clinical cases. They have unique microscopic morphologies. Species of Synechalbastrum, isolated as contaminants, are of interest since they can be mistaken for Aspergillus on casual inspection. Typical microscopic morphologies of these genera are shown in F2.

Treatment

Once diagnosis has been established, correction of hypoxia, acidosis, hyperglycemia, and electrolytic imbalance needs to be undertaken. Steroids, anti-metabolites, and immunosuppressive drugs should be discontinued, if possible. Aggressive surgical debridement is usually undertaken, along with high dose intravenous amphotericin B therapy (5mg/kg IV daily). Treatment is continued until remission is achieved. Liposomal amphotericin B may be more effective and less toxic. Resistance to amphotericin B has been observed with prolonged therapy.

Local irrigation and packing to aid delivery of amphotericin B to necrotic and poorly perfused tissues has been tried as an adjunct to therapy. This could help prevent disfiguring surgery.

Prognosis

The survival rate in patients with uncontrolled diabetes mellitus suffering from the rhinocerebral form is very grave. Patients with leukemia or lymphoma suffering from the pulmonary form usually die from the infection. The GI tract infection is usually diagnosed on autopsy.

The overall mortality is high, usually 30% to 70%. Death usually results in 2 weeks if untreated or unsuccessfully treated. The survival rate lowers as the diagnosis to treatment interval increases. Seventy percent of survivors have permanent residual effects, including blindness, cranial nerve defects, and surgical disfigurement.