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Mucormycosis

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Abstract

The zygomycoses are infections caused by fungi of the class zygomycetes, comprised of the orders Mucorales and Entomophthorales. Fungi of this order are causes of mucormycosis, an acute opportunistic infection occurring mostly in immunocompromised individuals, particularly in patients with diabetic ketoacidosis. The purpose of this paper is to present an academic perspective on the pathophysiology, presentation and management of mucormycosis. Possible management strategies are provided.

Keywords: amphotericin, diabetes ketoacidosis, mucormycosis, phycomycosis, zygomycosis

Introduction

Mucormycosis [1], also known as zygomycosis or phycomycosis was first described by Paultauf in 1885. He documented involvement of the central nervous system for the first time, and coined the term "mycosis mucorina" which later became "mucormycosis." In 1959, Lie-Kian-Joe, *et al.* [2] proposed that the disease be designated "phycomycosis" rather than "mucormycosis", since they found that fungi belonging to orders other than the Mucorales (such as Entomophthorales, Zoopagales and Kickxellales) were pathogenic to man. Since then the term phycomycosis has become widely accepted. The term "zygomycosis" includes both mucormycosis and entomophthoramycosis, the latter being a tropical infection of the subcutaneous tissue or paranasal sinuses caused by species of *Basidiobolus* or *Conidiobolus*.[3–5] Mucormycosis is the terminology that will be used for the sake of uniformity in this text, although zygomycosis and phycomycosis are also accepted. Mucormycosis is a rare but fatal or aggressive, opportunistic infection of the sinuses and brain caused by saprophytic aerobic fungi of the phycomycetes, order Mucorales.[3–5] Among the Mucorales, *Rhizopus* and *Mucor* are the common causes of human infections.

Phycomycetes (Zygomycetes) are common throughout the environment and in bread mould, soil, manure, decaying fruit and vegetables, and are frequently found colonizing the oral mucosa, nose, paranasal sinuses and throat, where massive spore formation occurs.[7, 8] Inhalation is the natural route of infection. Infection progresses as the hyphae begin to invade blood vessels and causes erosion of the bone through walls of the nasal and maxillary sinuses. Extension to ethmoid sinuses can lead to orbital and retro-orbital involvement. Intracranial involvement also occurs from invasion by way of the superior orbital fissure, ophthalmic vessels and cribriform plate, through the carotid artery or possibly via a perineural route.[7–10]

Pathogenesis

Host defences

Both mononuclear and polymorphonuclear phagocytes of the normal host are the major defence mechanism against mucormycosis. They kill Mucorales by the generation of oxidative metabolities and the cationic peptides defensins.[11–14] Organisms of this family of saprophytic fungi are ubiquitous, infecting humans whose systemic health is compromised (dysfunctional phagocytes). Several predisposing

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conditions, such as diabetes, leukemia, lymphoma, AIDS, chemotherapy, severe burns, malnutrition and uremia have been reported in the literature.[1–10]

Human infection is felt to be caused by asexual spore formation.[1] The tiny spores become airborne and land on the oral or nasal mucosal of humans. In the vast majority of immunologically competent individuals, these spores will be contained through phagocytic response. If this fails (for example, in immunocompromised or metabolic abnormalities), germination will ensue and hyphae will develop. Because polymorphonuclear leukocytes are less effective in removing hyphae, the infection can then become established. Hyperglycemia and acidosis are known to impair the ability of phagocytes to move toward and kill the invading organism by both oxidative and non-oxidative mechanisms (they provide an excellent environment for fungi to grow).[14]

Role of iron

Iron appears to be an important element in the growth factor of Mucorales. Reduced ability of the serum to bind iron at low pH may be the basic defect in the body defense mechanism.[1, 11, 15–17] Human resistance to fungal infection rests on the ability to restrict the availability of iron to an invading fungus by binding it to proteins such as apotransferrin. Fungal hyphae produce a substance called rhizoferrin which binds iron avidly. This iron-rhizoferrin complex is then taken up by the fungus and becomes available for vital intracellular processes, further reducing iron availability for the host.

Deferoxamine is used as a chelating agent for iron and aluminum in patients undergoing hemodialysis and has been associated with a fulminant form of mucormycosis.[1, 11, 18–2] While deferoxamine is an iron chelator from the perspective of the host, *Rhizopus* spp. actually utilizes deferoxamine as a rhizoferrin to supply previously unavailable iron to the fungus. Patients with diabetic ketoacidosis are at high risk of developing mucormycosis due to an elevation in available serum iron.[24]

Clinical presentation

The clinical hallmark of mucormycosis is vascular invasion resulting in thrombosis and tissue infarction (necrosis). Because of its lethal (aggressive) nature death can occur within several days to a few weeks, even when appropriate treatment has been instituted. Based on clinical presentation and the involvement of a particular site, mucormycosis can be divided into various clinical categories (rhinocerebral, pulmonary, cutaneous, gastrointestinal, disseminated and miscellaneous).

Rhinocerebral mucormycosis is the most common form of the infection and predominantly occurs in patients with poorly controlled diabetes mellitus. The high iron, glucose-rich acid milieu facilitates fungal growth.[1, 4, 10, 25,] Pulmonary mucormycosis occurs most commonly in leukemic patients who are receiving chemotherapy and patients undergoing hematopoietic stem cell transplants.[27–29] Pulmonary mucormycosis may develop as a result of inhalation or by hematogenous or lymphatic spread. Symptoms include dyspnea, cough and chest pain.[29] Gastrointestinal mucormycosis is rare but it is believed to occur in extremely malnourished children. The stomach, colon and ileum are the most commonly involved sites.[30] Hepatic mucormycosis has been associated with ingestion of herbal medications.[31] Nonspecific abdominal pain, nausea, vomiting, fever and hematochezia are the common symptoms. The agents of cutaneous mucormycosis are typically incapable of penetrating intact skin. Patients who develop cutaneous mucormycosis are those with disruption of the normal protective cutaneous barrier. However, burns and traumatic disruption of skin enable the organisms to penetrate into deeper tissues. Hematologenously disseminated mucormycosis may originate from any primary site of infection.[8, 11] Pulmonary mucormycosis in severely neutropenic patients has the highest incidence of dissemination. Less commonly, dissemination can arise from the gastrointestinal tract, sinuses or cutaneous lesions. The most common site of dissemination is the brain, but metastatic lesions may also be found in the spleen, heart, skin and other organs. Cerebral infection following dissemination is distinct from rhinocerebral mucormycosis and results in abscess formation and infarction, patients present with sudden onset of focal neurological deficits or coma.[11] Agents of the Mucorales may cause infection in virtually any body site.[1, 8, 11]

Other at-risk populations include immunosuppressed patients with organ transplants, possibly due to iron overload from repeated blood transfusion

and graft-versus-host disease treated with steroids, patients undergoing hematological stem cell transplantation and patients with severe burn.[1, 4, 10, 32-40] Other immunocompromised hosts, such as patients with AIDS, rarely have been reported with this disease.

Symptoms

Infection is acquired through the respiratory tract. In this text, only the infection occurring via the respiratory tract is discussed. Once the infection is established in the paranasal sinuses, the infection can easily spread to and enter the orbit via the nasolacrimal duct and medial orbit.[1] The ease of spread may be due to the thinness of the lamina papyracea and perforation of the medial wall by arteries and veins. Spread to the brain may occur via the orbital apex, orbital vessels or via the cribiform plate.[1, 9]

The initial symptoms are low-grade fever, sinusitis and eye and facial pain, followed by the onset of conjunctival suffusion, blurry vision and chemosis, superior orbital fissure syndrome (unilateral sensory deficit of the first and second divisions of the trigeminal nerve and ophthalmoplegia), proptosis due to vascular compromise and infection of the orbital contents.[26, 32–34] Fungal invasion of the globe or retinal artery leads to blindness.[32, 35-37] When the orbital apex becomes involved, extension into the cavernous sinus and involvement of the internal carotid artery can result in cerebral ischaemia, brain infarction and ultimately death.[9]

Diagnosis

Diagnosis of mucormycosis is established by clinical picture revealing the invasive course of the disease and by demonstrating fungal elements in smear, culture and histopathology.[35] Imaging studies play an important role in defining the extent of involvement and presence of intracranial disease.[38, 39] The most common finding on computerized tomography (CT) scanning of the head or sinuses is the soft tissue swelling, sinus mucosal thickening, bone erosion, thickening of extraocular muscles, intracranial/ cavernous sinus thrombosis, enhancement of vessels and central nervous system lesions. Magnetic resonance imaging (MRI) can add diagnostic information by showing the extension of the infection into the surrounding blood vessels, orbital fat and intracranial invasion before clinical signs develop.

Imaging techniques may be suggestive of mucormycosis but are rarely diagnostic because the initial imaging study is frequently negative or has subtle findings.[11] Diagnosing mucormycosis almost always requires histopathologic evidence of fungal invasion of the tissues. Culturing organisms from a potential infected site is rarely sufficient to establish the diagnosis of mucormycosis. The causative agent is ubiquitous, may colonize a normal person, and is a relatively frequent laboratory contamination. Additionally, the organism may be killed during tissue grinding, which is routinely used to process tissue specimens for culture,[1, 8, 11] thus a sterile culture does not rule out the infection. Furthermore, waiting for the results of the fungal culture may delay the institution of the appropriate therapy, where time is critical.

There are no reliable serologic, PCR-based or skin tests for mucormycosis. Therefore, the diagnosis should be made by biopsy of infected tissues. The biopsy should demonstrate the characteristic wide, ribbon-like, unseptate hyphae of uneven diameters that branch at right angles with long sporangiophores attached.[26, 32] Other fungi (Aspergillus, Fusarium or Scedosporium) may look similar to the Mucorales on biopsy, however, they have septate, thinner and branching at acute angles.[40]

Treatment

Four factors are critical for treating mucormycosis:

Rapidity of diagnosis

Early diagnosis is important because small, focal lesions can often be surgically excised before they progress to involve critical structures or disseminate.[26, 37] A high index of clinical suspicion is critical and to aggressively pursue diagnostic biopsy. Given the rapidly progressive nature of mucormycosis and marked increase in mortality when the fungus penetrates the cranium, any diabetic patient with a headache, visual changes and eye pain is a candidate for prompt evaluation with imaging studies and nasal endoscopy to rule out mucormycosis.[10]

Reversal of the underlying predisposing factors

Correcting or controlling predisposing problems is also essential for improving the treatment outcome. In diabetic ketoacidotic patients, hyperglycemia and acidemia should be corrected.

Discontinuation of deferoxamine or immunosuppressive therepy, particularly steroids, should be strongly considered when the diagnosis of mucormycosis is made.

Appropriate antifungal therapy

The current available antifungal agents lack significant clinical trial data because it is impractical to conduct prospective interventional study. Even though the disease is unusually deadly, it occurs at a low frequency relative to other opportunistic infections. Given the lack of controlled clinical trials for mucormycosis, clinicians have been forced to rely on anecdotal case reports and limited retrospective reviews in determining the first-line therapy for mucormycosis. Until recently, only members of the polyene antimicrobial class demonstrated activity against the agent of mucormycosis.[1,8,11,32] These include Amphotericin B deoxycholate (AmB), Liposomal amphotericin B (LAmB) and Amphotericin B lipid complex (ABLC).

AmB acts by binding to sterols (primarily ergosterol) in the fungal cell membrane with a resulting change in membrane permeability. LAmB is highly protein bound and poorly dialyzed. Small doses administered over a long period help to minimize toxicity and side effects. Recognized side effects are fever, chills, headache, malaise, nausea, vomiting, phlebitis and nephrotoxic.[1,8,11,37] ABLC is a formulation designed to be less toxic than AmB, while enhancing the therapeutic index of the drug.[1]

Appropriate surgical and debridement of infected tissue

Fungi strive in necrotic tissue and surgery is necessary due to the massive amount of tissue necrosis occurring during mucormycosis. Early surgical excision of the infected sinuses and appropriate debridement of the retro-orbital space can often prevent the infection from extending into the eye. Repeated surgical debridement may be necessary to ensure that all necrotic tissue has been debrided and the infection has not progressed.[26]

Orbital exenteration may be life-saving in the presence of an active fungal invasion of the orbit and should be considered for an actively infected orbit with a blind and immovable eye.

Novel therapies

The central role of iron metabolism in the pathogenesis of mucormycosis suggests the possibility of utilizing effective iron chelators as adjunctive antifungal therapy. The potential for this iron chelator to serve as adjunctive therapy with other antifungal agents should be investigated. Hyperbaric oxygen should be used to treat mucormycosis because higher oxygen pressure improves the ability of the neutrophils to kill the organisms. High oxygen pressure inhibits the germination of fungal spores and growth of mycelia.[43] Cytokines that activate phagocytic activity (such as gamma interferon and granulocyte-macrophage colony-stimulating factor) increase the ability of phagocytes to kill.[11, 44] Whether these therapies could improve the outcomes of patients with mucormycosis need to be established through appropriate controlled prospective clinical trials.

Prognosis

Despite advances in diagnosis and treatment, a high mortality still exists for this disease. Death may occur within two weeks if untreated or unsuccessfully treated. Although the mortality rate is high, the infection can be cured when diagnosed early and treated with antifungal agents and aggressive surgery.

Conclusion

Early recognition and treatment are essential for this disease. The management demands a multidisciplinary approach. ophthalmologists, optometrists, physicians, maxillofacial surgeons, oculoplastic surgeons, neurosurgeons and otolaryngologists. Current regimen for the treatment of mucormycosis is amphotericin and surgery. In the future, iron chelator, hyperbaric oxygen and cytokine therapies may be useful as adjunctive to standard antifungal
therapy.

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