Rhino-orbital-cerebral Mucormycosis

Siriorn Watcharananan, M.D.,
Prawat Chantharit, B.Sc.(Pharm), M.D.

INTRODUCTION

Mucormycosis (previously called, Zygomycosis) is a known type of an aggressive fungal infection. Recently, it has become increasingly more common with an unacceptably high mortality despite first-line antifungal therapy. Rhino-orbital-cerebral mucormycosis (ROCM), consisting of involvement of sinuses with or without brain/orbits, has accounted for up to half of all cases of mucormycosis.1 With a recent change in the epidemiological trend of the invasive fungal infection, as well as an advance in the knowledge of the pathogenesis of the infection, we aimed to summarize and update the recent knowledge of mucormycosis, focusing on the rhino-orbital-cerebral involvement and the management strategy which potentially improves the treatment outcome of this infection.

Microbiology

In the past, this fungal infection was generally accepted as “Zygomycosis”. However, from the recent reclassification, the order Zygomycetes has been eliminated and in stead, the order Mucorales is now placed in the subphylum Mucormycotina. The fungal organisms in the Mucorales encompass several fungal species, which include Rhizopus, Rhizomucor, Mucor, Absidia spp. Rhizopus oryzae (arrhizus) is the most common cause of mucormycosis. However, the use of more advanced diagnostic tools, other species have been identified; for example Apophysomyces, Cunninghamella, Saksenaea, Cokeromyces, Syncephalastrum spp.

Pathogenesis and Risk Factors of Mucormycosis

The agents of mucormycosis are ubiquitous in soil and decaying vegetation. Acquisition of the fungal organism is mainly by inhalation or ingestion of spores which subsequently results in deposition of the fungus in paranasal sinuses. Although less common, contamination of wounds with sporangiospores from the environment is another source of entry.2 Following the initial entry, the fungus subsequently dissects and causes angioinvasion within internal elastic lamina of the artery. This results in thromboembolism, endothelial damage, and tissue ischemia/necrosis. The infarct tissue further enhances fungal proliferation and as a result of the poor vascular supply, eradication of the fungus by systemic medical therapy seems difficult. For ROCM, upon germination in paranasal sinuses, the fungus could further propagate to adjacent structure, depending on the location of spore deposition. Maxillary sinus is the most common second deposition site which occurred by the direct fungal spread inferiorly. Other sites include invasion of the nearby structure, include
the palate, posterior to sphenoid sinus and beyond into the cavernous sinus. The orbit extension can also occur via the nasolacrimal duct, medial wall dehiscences and anterior or posterior ethmoid orifices. Brain is usually affected through the direct fungal invasion into the orbital apex, orbit vessel, internal carotid thrombosis or the cribiform plate.

Phagocytes are the major host defense mechanism against mucormycosis. From clinical evidence, neutropenic patients or patients with dysfunction of phagocytes are at higher risk of developing mucormycosis. Neutrophil is critical for initiation and execution of the acute inflammatory response. Neutrophils together with macrophages internalize conidia and use respiratory burst to control the infection. Although the ingestion of the fungal organism is not possible due to the large size of its hyphae, the fungus was damaged and subsequently destroyed. For neutropenic patients, duration of neutropenia and low level of circulating neutrophils might then be important factors that might potentially be reversible targets by using of colony-stimulating factors. From a recent large-scale literature review by Roden et al., diabetes mellitus and malignancy are the two major co-morbid conditions among patients diagnosed with mucormycosis. This population becomes susceptible to the infection due to elevated available serum iron, especially during diabetic ketoacidosis (DKA). Apart from DKA, risk factors for mucormycosis include hematological malignancy, solid organ/bone marrow transplantation, prior use of corticosteroid, injection drug use, deferoxamine therapy, renal failure, diarrhea/malnutrition, HIV infection and low-birth weight infant. During the status of DKA, neutrophils function is impaired, resulting in inability to prevent spore germination. In addition, there is an enhancement in the liberation of iron from iron-binding protein during the acidic environment. This iron is necessary for a wide range of cellular oxidation-reduction reaction. Fungi can chelate iron with their siderophores or another siderophore secreted by other organism (xenosiderophores) or both. By iron acquisition, deferoxamine can act as xenosiderophores, thus enhances delivery of iron to Mucorales spp., resulting in the proliferation of the fungus. The use of iron chelator and the status of iron overload are therefore risk factors of mucormycosis.

Epidemiology of Mucormycosis

Cases of mucormycosis are usually sporadic and occur worldwide. Nevertheless, local out breaks of mucormycosis have been reported, some of which were associated with constructions and use of adhesive tape. In the United States, an annual incidence rate was 1.7 infections per million populations. However, this infection has emerged as an increasingly significant cause of invasive mycosis over the past decades. According to the aforementioned study by Roden et al., the percentage of culture proven cases of mucormycosis has been rising significantly over the past 30 years. Of interest, their study also showed that the fungi potentially cause an invasive infection in a heterogenous population. Although majority of the cases were patients with diabetes mellitus (36%) and immunocompromised hosts (30%), approximately 20% of cases had no co-morbid condition. Recently, a rising number of cases have been shown following use of voriconazole for fungal prophylaxis. However, whether this antifungal agent is the risk factor for mucormycosis remains controversial.

Clinical Presentation and Outcome of Mucormycosis

The clinical presentation of this infection is quite similar to other invasive mould infection. Both mucormycosis and invasive aspergillosis can cause angioinvasion and tissue infarction. The most common
type of infections includes ROCM (39%), pulmonary (24%) and cutaneous (19%). According to the type of ROCM, rhino-cerebral involvement is usually the most common (21%), followed by sino-orbital (8%) and sinusitis (8%). Apart from ROCM, other forms of mucormycosis that are noteworthy includes pulmonary and cerebral mucormycosis. Although pulmonary mucormycosis occurred less frequently than ROCM, it was noted in a high proportion among immunocompromised patients (over 50%) which include those with malignancy, solid organ/bone marrow transplant recipients and patients who received deferoxamine therapy (28%). Cerebral mucormycosis occurred exclusively among intravenous drug users. Within this population, the cerebral involvement was the most common presenting pattern, reflecting hematogenous acquisition and was seldom associated with rhinocerebral infection. Both rhinocerebral infection and localized cerebral infection were associated with a mortality of 62%.

The survival analysis demonstrated that overall mortality improved from 84% in the 1950s to 47% in the 1990s. But their mortality due to mucormycosis has remained unchanged significantly since the 1960s despite amphotericin B deoxycholate being widely introduced. The significant risk factors for mortality were disseminated disease, renal failure and Cunninghamella species infection. Contrary to type 1 diabetes and no underlying condition which was independently associated with a reduced risk of death. Patients with surgical intervention were also significantly more likely to survive. According to the site of infection and mortality, pulmonary, rhinocerebral, kidney and gastrointestinal infection were associated with the highest risks of mortality. Among healthy individual who were diagnosed with mucormycosis, invasive infection was not uncommon and mortality rate was 35%.

Sign and Symptoms of ROCM

The initial clinical findings are sinusitis or periorbital cellulitis, facial pain and numbness, blurred vision, conjunctival suffusion and soft tissue swelling. Headache, noisy breathing, odontalgia, maxillary pain and hyposmia or anosmia may be seen. Necrotic eschars are the feature of aggressive angioinvasive infections and can be found in nasal cavity, nasal turbinates, facial lesion and palate. Orbital lesion can extend to preseptal and orbital cellulitis which associates with blurred vision, ophthalmoplegia, eyelid edema and proptosis. Sagittal sinus thrombosis and epidural or subdural abscess formation are rarely intracranial complication. Blindness is usually the result of optic nerve invasion or cavernous sinus thrombosis. Cranial nerves V and VII involvement may cause ipsilateral loss of facial sensation, ptosis and pupillary dilatation. Bloody nasal discharge may be the first sign of brain invasion through turbinates. Cerebral vascular invasion may lead to disseminated infection with or without mycotic aneurysms formation.

Radiographic finding of ROCM

Contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) is an important diagnostic tool. CT is proper for bone and periorbital tissue destruction study, including edematous mucosa. But bony destruction is often seen later following development of tissue necrosis. MRI is useful modality for intradural and intracranial study especially vascular structure such as cavernous portion of the internal carotid artery. MRI is more sensitive than CT scan for detection of soft tissue extension. Most of the patients have isointense lesion relative to brain in T1-weighted images. The signal intensity in T2-weighted images is more variable. A pattern of anatomic involvement affects the nasal cavity, maxillary sinus, orbit and ethmoid cells.
However patients with early disease may have normal MRI and CT scans.\textsuperscript{11}

**Laboratory Diagnosis**

Currently, the most rapid diagnostic tool remains based upon direct identification of fungal hyphae from clinical specimen which is usually seen as broad, ribbon-like structure. However, the organism can sometimes be noted as pauciseptate hyphae. These fungi grow rapidly on Sabouraud dextrose agar but sporulation and identification may still take several days. The zygomycetous pathogens *Apophysomyces elegans* and *Saksenaea vasiformis* usually fail to sporulate on this routine mycological media. Padhye AA\textsuperscript{12} recommended placing the colonies of mycelial growth on distilled water with yeast extract solution. Until now, the standard diagnosis of Mucorales is still the finding from histopathology and cultures. Use of molecular testing has remained an area of ongoing study. Seanne P et al\textsuperscript{13} found that real-time PCR technique had shorter turnaround time, good specificity (100\%) and sensitivity (92\%).

**Management strategies**

**Surgical intervention**

Early and aggressive surgical debridement of infected tissue around craniofacial structures is the cornerstone of treatment. Extensive resection of involved tissue should be done, including muscle, skin of the nose, all involved sinus, infratemporal fossa, temporal area and orbital exenteration that is life-saving in the case of active fungal invasion of the orbit.\textsuperscript{3} The key to successful treatment is the ability to recognize the early sign and symptom and correction of active underlying medical condition. However, it is difficult to achieve these purposes completely because important structures are often adjacent to necrotic tissues and there are variables among different countries for accessing the effective antifungal agents.

**Primary antifungal therapy**

Amphotericin B is the primary agent for mucormycosis. The optimal dosage is 1 mg/kg/day.\textsuperscript{14} For ROCM, longer duration of amphotericin B is generally required. However, the treatment is usually limited by side-effects, particularly nephrotoxicity. Nowadays, the side effects could be minimized by use of lipid formulations of amphotericin B. Other than benefit from less side effects, lipid formulation amphotericin B is preferred for ROCM because of its higher central nervous system penetration and it lasts longer in the vasculature, resulting in an increased capillary permeability and greater concentrations in tissues.\textsuperscript{3} The recommended dose of liposomal amphotericin B is 5-7.5 mg/kg/day. In the case of cerebral lesion, increasing the dosage of liposomal amphoterin B to 10 mg/kg/day may be considered based on the limited polyene penetration into the brain.\textsuperscript{14} The role of combination therapy of liposomal amphotericin B plus posaconazole as primary treatment for ROCM is insufficient to support as general recommendation. In contrast, preclinical data support the addition of deferasirox to initial liposomal amphotericin B therapy, particularly for central nervous system infection in diabetic patients.

**Salvage therapy**

Successful outcomes of posaconazole administered in conjunction with amphotericin B have been seen in patients with ROCM and in a combined heart-kidney transplant patient who previously failed amphotericin B.\textsuperscript{15} Greenberg RN et al\textsuperscript{16} have published non-randomized compassionate use programs evaluating salvage treatment with posaconazole oral suspension 200 mg administered four times per day or
400 mg twice per day. Thirteen of twenty-four patients had rhinocerebral infection and the median treatment duration was 182 days. The 90-day survival rates were 82.8% from mucormycosis and 78.4% from all causes of death. Posaconazole oral solution was generally well tolerated. Jo Anne H et al. have reviewed retrospectively 91 cases with mucormycosis that were refractory to prior antifungal treatment (81 cases) or were intolerant of such treatment (10 cases) and participated in the compassionate-use posaconazole (800 mg/day) program. From 81 cases, there were 42 cases as sinus infection, 11 cases as brain infection and 11 cases as orbital infection. Number of patients with successful treatment after 12 weeks of posaconazole treatment for each site of infection were 23, 8 and 5 patients respectively. The overall rate of complete or partial response was 60% at 12 weeks.

It is now clear that iron metabolism plays a central role in regulating mucormycosis infections and that deferoxamine predisposes patients to mucormycosis by inappropriately supplying the fungus with iron. Recently, experimental studies (references of both in vitro and animal models) showed that new iron chelators, including deferriprone (DFP) and deferasirox (DFX) exhibited activity against various isolates of *Mucorales* spp. These agents do not act as xenosiderophores and the fungi cannot detach iron molecule from them. In contrast, these two agents are probably capable of detaching iron from the fungal uptake molecules and holding it more strongly. Reed et al. reported the first case of mucormycosis being treated with a combination of classical antifungal treatment and iron chelator. Based on their study, a 40-year-old diabetic patient suffered from an aggressive rhinocerebral mucormycosis and progressive central nervous system involvement despite a combination of high-dose liposomal amphotericin B and caspofungin with surgical debridement. Brain magnetic resonance imaging showed new parenchymal lesions and left cavernous sinus thrombosis. The salvage treatment with deferasirox 1,000 mg/day was administered for 7 days. A new brain magnetic resonance imaging scan showed significant improvement without recurrent infection. Based on preclinical studies of non-iron-overload primates salvage therapy with deferasirox should only be used for 2-4 weeks because a higher potential of deferasirox toxicity if the drug was exposed for longer than 4 weeks. The other promising agent for mucormycosis is echinocandin. Base on molecular studies, *Rhizopus oryzae* also had FKS gene that encoded 1,3-β-D-glucan synthase which was inhibited by echinocandin. In DKA mice infected with *Rhizopus oryzae*, combination of amphotericin B lipid complex (ABLC) and caspofungin regimen also improved survival compared to either monotherapy or placebo. Apart from caspofungin, combination therapy with liposomal amphotericin B (LAmB) plus either micafungin or anidulafungin also had synergistic activity in either neutropenic or DKA mice with disseminated mucormycosis. Other than antifungal agents and newer iron chelators, hyperbaric oxygen therapy is another tool, which might be preserved for deteriorating case. Hyperbaric oxygen exerts a fungistatic effect and enhances neovascularization with subsequent healing in poorly perfused acidic and hypoxic tissue. This treatment should consist of exposure to 100% oxygen for 90 minute to 2 hours, under pressure of 2.0-2.5 atmospheres with one or two exposures daily for a total of 40 treatments. Other ancillary option for treatment is recombinant
cytokines; granulocyte stimulating factor, which potentially help increasing host response by augmenting the neutrophil killing function against hyphal elements. However, such treatment modality remains controversial as there is currently limited clinical data.

CONCLUSION

Rhino-orbital-cerebral mucormycosis has a higher survival rate than dose pulmonary or disseminated mucormycosis due to being frequently detected earlier and the most common underlying cause, diabetic ketoacidosis, can be treated readily. Early diagnosis with prompt surgical debridement and proper antifungal regimen are the reasonable strategies that can affect morbidity and mortality. Another aspect are to control underlying diseases and serial imaging modality, all of these factors will determine the total duration of therapy. Lipid formulations of amphotericin B are preferred agents as primary therapy due to less toxicity and prolonged duration of treatment. Early combination of lipid formulation amphotericin B with iron chelator is waiting for DEFEAT Mucor clinical trial to clarify the safety and effectiveness of this combination. Posaconazole is another agent for salvage therapy in the case of failure to initial regimen, by using alone or combination with standard regimen. However, this issue requires for further study in the large clinical setting.

References

13. Hata DJ, Buckwalter SP, Pritt BS, Roberts GD, Wengenack NL. Real-time PCR method for


