Rhinomaxillary mucormycosis – Current perspectives in diagnosis and management

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Introduction

Mucormycosis is an opportunistic infection often caused by a saprophytic fungus, Mucoromycotina. Six forms of invasive mucormycosis have been previously described – rhinocerebral, pulmonary, cutaneous, gastrointestinal, disseminated type, and miscellaneous. [1] Rhinocerebral is the most common form of the disease. Those at risk include patients who are neutropenic have acquired immunodeficiency syndrome, post-organ transplant and those who suffer from uncontrolled diabetes mellitus, among other immunocompromised patients. The key to diagnosis and appropriate management of mucormycosis is to have a high index of suspicion when presented with oral or sinus symptoms in immunocompromised patients.

Rhinomaxillary Mucormycosis

Mucormycosis is a rapidly spreading fungal infection caused by fungi that belong to the order Mucorales and subphylum mucormycotina. [2] These fungi are found commonly in soil and organic matter and generally are introduced into humans through inhalation of the spores. These fungi cause mucormycosis, a life-threatening fungal infection almost universally affecting immunocompromised hosts. [1] Among the Mucorales, Rhizopus oryzae and Mucor are by far the most commonly isolated species in human disease, especially in rhinocerebral and rhinomaxillary mucormycosis. [3,4] Data from clinical and experimental studies have demonstrated that impaired phagocyte function is one of the most important factors in increasing susceptibility to mucormycosis. Polymorphonuclear and mononuclear phagocytes of normal hosts kill Mucorales by the generation of oxidative metabolites and the cationic peptides defensins. [4] Phagocytic impairment can be caused by a variety of diseases and metabolic derangements. Neutropenic patients obviously have a paucity of phagocytes to fight the fungi. Steroid use has also been shown in mouse studies to impair bronchoalveolar macrophage ability to prevent germination of the spores of Rhizopus. [5] Hyperglycemia and acidosis are known to impair the ability of phagocytes to attach and kill the organisms, although the mechanisms of how they impair phagocyte function are still unknown. In developing countries like India, the most common cause of immunocompromise predisposing to mucormycosis is uncontrolled diabetes mellitus. [6] In a recent report of 10 cases from India, all patients had uncontrolled diabetes mellitus. [7]

Pathogenesis

A key feature of the pathogenesis of mucormycosis is the extensive angioinvasion with resultant vessel thrombosis and tissue necrosis which are hallmarks of the disease. This angioinvasion is associated with the ability of the organism for...
Patel, et al. Rhinomaxillary mucormycosis

Hematogenous spread from the primary infection site to cause sepsis. Interestingly, even if the Rhizopus oryzae cells are killed by antifungal treatment, phagocytosis of the dead Rhizopus by endothelial cells causes persistent endothelial cell damage.

This is likely the reason why antifungal therapy alone is inadequate to control the disease, but aggressive debridement is needed to remove even the dead fungi to avoid further tissue destruction and necrosis.

Rhinocerebral mucormycosis is the most common form of the disease, accounting for approximately one-third to one-half of all cases of mucormycosis. Rhino-orbital-cerebral and rhinomaxillary mucormycosis appear to be used synonymously in the literature; however, the authors feel that they should be considered somewhat separately, although the terms are used interchangeably in the literature. Although both have a poor prognosis and high mortality rate, rhino-orbital should be used to describe a more aggressive form because of its close proximity to the skull base, hence, cerebral involvement is more likely to occur more rapidly. Both lead to widespread maxillary and midfacial necrosis due to the involvement of the sphenopalatine and internal maxillary arteries. The images included in this paper demonstrate a case of rhinomaxillary mucormycosis treated successfully with a partial maxillectomy. Rhino-orbital-cerebral would have required a much more extensive operation and been less likely to lead to control of the disease.

Clinical Features

Early diagnosis of mucormycosis requires the clinicians to have a high index of suspicion for the condition when presented with oral or sinus symptoms in an immunocompromised host. Up to half of all cases of mycoses are diagnosed postmortem, showing the difficulty in early diagnosis. Clinical symptoms of the rhinocerebral form are highly variable. Patients can present with a variety of symptoms including sinusitis symptoms, facial and periorbital swelling, palatal ulceration, gingival ulceration, facial paresthesia or weakness, and odontogenic pain. These non-specific symptoms in an immunocompromised patient should guide the clinician to need to exclude mucormycosis urgently. Necrosis of the palate or turbinates should be regarded as almost pathognomonic of mucormycosis and should prompt urgent biopsy. Systemic signs such as fever are highly variable and may be absent in up to half of cases. Once spread into the orbit, patients often develop blurry vision, ophthalmoplegia and proptosis, and ultimately loss of vision. These are late signs and imply a very poor prognosis even with aggressive treatment. Once there is extensive central nervous system involvement, the angioinvasive nature of the disease leads to cavernous sinus thrombosis, cerebral infarctions, and ultimately death.

Diagnosis

Diagnosis can be challenging. There are no reliable serological, polymerase chain reaction, or skin tests available for mucormycosis. Imaging with a computed tomography (CT) or magnetic resonance imaging often shows non-specific changes and can suggest, but not confirm the presence of mucormycosis. As demonstrated in Figure 2, initial imaging showed no bony destruction, but some non-specific sinus changes. Bony changes were seen on subsequent CT 4 days later and were considered as a late change. Diagnosis requires biopsy confirmation of the fungi and significant angioinvasion with widespread necrosis. The hyphae of the Mucorales are often non-septate, with wide ribbon-shaped hyphae. The hyphae often show branching at right angles but ranging from 45° to 90° [Figure 3]. Hence, in immunocompromised patients, aggressive debridement is often necessary.

Figure 1: Necrotic region in palatal of the maxillary left quadrant at initial presentation in a neutropenic patient diagnosed with recurrent acute myeloid leukemia. The second photograph shows the lesion 4 days later demonstrating the rapid progression of the necrotic area.

Figure 2: Initial CT sinuses at presentation can show only mild sinus changes which are non-specific. The second image shows the progression after 4 days demonstrating the significant progression of sinus inflammatory changes approximating the orbital cavity, with evidence of bony destruction of the lateral nasal wall and maxilla.

Figure 3: Branching pattern of Rhizopus oryzae characterized by non-septate, wide ribbon-shaped hyphae, with some branching ranging from 45° to 90°.
Figure 4: Aggressive debridement of the lesion with alveolectomy and functional endoscopic sinus surgery was performed in this case, which led to the resolution of the infection before the infection extending to the orbit and skull base. The oroantral defect was closed with an obturator needed to confirm the diagnosis. In the above-reported case, due to the subtle clinical changes, a biopsy was performed first before formal debridement to confirm the diagnosis because of the patients’ thrombocytopenia preventing urgent immediate debridement.

Treatment

Treatment involves several key factors in the following order: Reversal of the underlying predisposing condition if possible, antifungal therapy and aggressive surgical debridement. Stopping steroids and correction of acidemia should be commenced hand in hand with starting antifungal therapy. Choosing the ideal antifungal therapy is difficult due to the paucity of evidence and the lack of available clinical trials. Despite the availability of a variety of antifungal agents, the susceptibility of various strains of Mucorales makes choosing empirical therapy very challenging. Combination therapy with a polype like amphotericin B at a dose of 1 mg/kg/day combined with an echinocandin (like caspofungin) or an azole like isavuconazole can be considered; however, no clinical trials are available to confirm the ideal combination therapy. Consulting the microbiology and infectious diseases team for antifungal advice is prudent, and it is important to consider the patients’ comorbidities to minimize toxicity. In the literature so far, a combination of a polype and an echinocandin appears to be the most effective combination therapy. Antifungal therapy alone is unlikely to be effective without surgical debridement [Figure 4]. Even if the fungus appears susceptible in vitro, due to the extensive angioinvasion and necrosis, the penetration of the anti-infective agents to the site of infection is likely to be poor. Aggressive surgical debridement of all affected tissue is vital and significantly improves outcomes. In a case series of 49 patients with rhinocerebral mucormycosis, the mortality rate with antifungal therapy alone was 70% compared with 14% for those treated with a combination of antifungal therapy and surgery. The surgeon needs to be aggressive, debriding all affected tissue, which may require a maxillectomy and orbital exenteration when orbital involvement is found.

Adjunctive therapies suggested in the literature include the use of hyperbaric oxygen and cytokine therapy. The use of these adjunctive therapies has only been reported in isolated case reports and small case series. Further research is needed to determine the efficacy of these adjunctive therapies in addition to antifungal therapy and surgical debridement.

Conclusion

Mucormycosis is a potentially fatal fungal infection and is becoming increasingly more common in immunocompromised patients. Although no clear treatment protocols are available due to the paucity of evidence, the main principles of the management remain the same in all cases. Early diagnosis, treatment of underlying cause where possible, combination antifungal therapy, and aggressive surgical debridement are the mainstays of treatment. Clinicians should have a high index of suspicion for mucormycosis in all immunocompromised patients presenting with non-specific sinus, orbital, or oral symptoms.

Declaration of Patient Consent

The patient whose images were used in this report gave informed consent for his case to be presented and photos and findings to be published.

Conflicts of Interest

None.

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