Mucormycosis-A Formidable Challenge

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The term ‘Mucormycosis’ should be used to describe the disease caused by fungi with large, irregular, ribbon-like, sparsely septate hyphae in the setting of a compatible clinical syndrome. The term ‘Zygomycosis’ should no longer be used as the class ‘Zygomycetes’ has been abolished.1 Mucormycosis has emerged as an important infection due to the growing population of immunocompromised hosts and the advent of effective antifungal agents against Candida and Aspergillus. This issue carries an important study on mucormycosis from a tertiary care centre in South India.

The diagnosis of mucormycosis relies both on histopathological and microbiological examination. Because of the ubiquitous nature of these fungi in the environment, positive cultures may occasionally reflect colonisation or culture contamination rather than true infection. Hence, histopathological documentation of fungal invasion, especially angioinvasion, is important. However, culture is a must to distinguish Mucorales from other fungi with similar morphology like Entomophthorales and for identification to the genus and species level. Culture recovery of the agents of mucormycosis is inherently poor owing to the friability of the non-septate hyphae making them more susceptible to damage during tissue manipulation. Recovery can be improved by mincing (not homogenizing) tissue and using culture techniques that stimulate in vivo growth such as incubation at 35-37°C in semi anaerobic conditions. Hence clinicians should inform the microbiology laboratory about the suspicion of mucormycosis.1,2

Pulmonary mucormycosis is usually associated with a high mortality (50-70%, increasing to 95% with extrathoracic dissemination). It was heartening to note that 2 of the 3 patients with pulmonary mucormycosis in the present study survived. Pulmonary mucormycosis needs to be distinguished from the other more common mould diseases such as invasive pulmonary aspergillosis. They are clinically difficult to distinguish and timely diagnosis is a critical factor in the outcome because first line antifungals typically used for aspergillosis such as voriconazole, lack activity against Mucorales. Clues for distinguishing pulmonary mucormycosis from aspergillosis may include presence of severe sinusitis, prophylaxis with antifungals that possess activity against aspergillosis but not mucormycosis (e.g., voriconazole); presence of ≥10 nodules, pleural effusion and reverse halo sign (focal round area of ground glass attenuation surrounded by a ring consolidation) on CT scan, and possibly the repeated absence of Aspergillus galactomannan antigen in the serum.1,3

Both the patients of pulmonary mucormycosis who survived had been treated with a combination of surgery and amphotericin B (AMB) whereas the one who expired was managed only with AMB. This highlights the role of surgical debridement in the management of mucormycosis along with antifungal agents. Angioinvasion, thrombosis and tissue necrosis associated with mucormycosis lead to poor penetration of the drugs at the site of infection. Hence debridement of necrotic tissues plays a critical role. The lipid formulations of AMB, particularly liposomal AMB, may be a better option as compared to amphotericin B-deoxycholate for transplant recipients, central nervous system infections and for those who can afford it. This is in view of fewer nephrotoxic effects, better brain penetration, reduction of fungal burden and immunomodulatory effects of liposomal formulations.3 Posaconazole, though not recommended as a primary therapy, is suitable as stepdown or salvage treatment. The possible availability of an intravenous formulation in future could make posaconazole a more appealing first line option, as the drug’s erratic bioavailability is the principle limiting factor influencing attainment of therapeutic blood levels during the first week of therapy.2

Management of mucormycosis becomes even more difficult when surgery is either impossible or incomplete. The role of adjunct treatment in the management of such cases becomes important for impeding fungal proliferation, improving tissue viability and improving host immunity.1,3 Echinocandins, generally not considered active against Mucorales, exhibit synergy with polyenes. The proposed mechanisms are improved polyene delivery to the cell membrane after disruption of β-D-glucan in the cell wall by the echinocandins; and increased exposure of the immunogenic epitopes on the fungal cell wall enhancing immune system recognition and hyphal damage.1 Hyperbaric oxygen exerts antifungal effects via improved neutrophil activity and improved rate of wound healing by increasing the release of tissue growth factors. Multiple immune augmentation strategies like granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor and interferon-γ have been found to be useful in enhancing the phagocytic activity. The role of deferasirox, an iron chelator without xenosiderophore activity in Mucorales, was emphasized in a recent case series from our centre.4 Deferasirox starves the fungus of iron which is critical for its growth and pathogenicity. Other agents with possible usefulness mentioned in the literature are colistin, statins, calcineurin inhibitors (tacrolimus and cyclosporine) and mTOR inhibitors (sirolimus and everolimus).

Mucormycosis still remains a rare disease and is not well understood by the general medical community. However, it has a high mortality, high morbidity and disfigurement among survivors, and the principles of management need to be clearly understood. While the case series from the authors’ centre serves to highlight the problem, only 27 cases out of 200 could be included due to completeness of records. It is possible that the other 173 cases had some clinical features which would be of importance to the clinicians. In this perhaps, there is a message for all centres in our country to have complete and reliable medical records. A registry of cases of mucormycosis will go a long way in assessing the risk factors and formulating diagnostic and management strategies for our country.

References

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