EDITORIAL

Post COVID-19 Mucormycosis in the Second Wave-Realities, Uncertainties and Myths

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After our last editorial on COVID-19-associated mucormycosis (CAM) in the Jan 2021 issue of this journal, there has been an exponential rise in CAM from nearly every part of the country. Although the true incidence is difficult to estimate given the rampant second COVID-19 surge and the ambiguity of a true denominator, the socioeconomic impact on the population and the health system has been devastating. The sensationalized misnomer of ‘black fungus,’ although taxonomically incorrect, paints a symbolic picture of the diabolical nature of invasive mucormycosis.

Myriad hypotheses have been generated for the inordinate number of cases in our country. Higher fungal spore counts in our tropical climate especially around heaps of garbage, construction of makeshift COVID-19 facilities, contamination of oxygen supplies, respiratory equipment, reused face masks and zinc supplements are some of the theories that have been deliberated upon inconclusively. The most convincing risk factors appear to be unrecognized, uncontrolled diabetes compounded by the indiscriminate use of steroids at high doses for prolonged periods, even in non-hypoxic patients. Such patients have spent most time in the community with all the heavy exposures that go with it. These cases may be considered as ‘Never in the frying pan, straight into the fire.’

A multicenter study of 187 cases of CAM after the first COVID wave, noted a 2.1-fold increase in the cases of mucormycosis during the peak COVID-19 period as compared to pre-COVID-19 time. Uncontrolled diabetes was noted in 62.7% of cases. COVID-19 was the only risk factor in 32.6% CAM patients among whom 78.2% received glucocorticoid treatment for COVID-19 management. Inappropriate glucocorticoid use was independently associated with late CAM.¹ Lymphocytopenia with prolonged depletion of T cell subsets is an important feature in COVID-19.² This is a known risk factor for opportunistic infections including invasive mucormycosis. Additionally hyperglycemia due to affection of the β-cells of the pancreas by SARS-CoV-2 may be a contributing factor.³

While rhino-orbito-cerebral involvement has been the most common manifestation even in pre-COVID times,⁴ dental pain, loosening of teeth and involvement of the jaw appear to be common features of CAM observed in the present outbreak.¹ Pulmonary CAM is less common, appears to affect patients with severe COVID 19 infection and poses significant diagnostic difficulties. Mixed infections with septate and aseptate moulds, both in the sinuses and lungs have also been reported.¹

Radical and often repeated surgical debridement has been the cornerstone of management for invasive mucormycosis. The benefits appear to be time sensitive and have dramatically improved survival in various studies, albeit limited by their observational, retrospective nature and small numbers.⁵ The aggressive approach to remove necrotic tissue and afford better antifungal penetration and oxygenation to the affected sites, forms the justification for radical surgery although resulting in mutilation and functional impairment. The advent of more effective treatment options like liposomal Amphotericin B (LAmB) and the newer oral Azoles, have emboldened treating teams to sometimes steer away from aggressive surgical approaches. Functional endoscopic sinus surgery for both tissue diagnosis and thorough debridement of sino-nasal disease remains the mainstay of surgical management. However, in cases with limited orbital involvement and preserved vision, medial orbital wall resection with orbital decompensation and retrobulbar Amphotericin B (AmB) injections have shown initial encouraging results. Organ and tissue sparing approaches are difficult decisions, requiring multidisciplinary expertise and close monitoring. Needless to emphasize that orbital exenteration is warranted in cases with extensive initial orbital involvement or with worsening of disease after attempted conservative management.⁶

AmB has been grand-fathered into the treatment of invasive fungal infections when there was no other drug available. All subsequent drugs have been compared to this standard. Over the years, AmB deoxycholate has been replaced by lipid formulations, in particular LAmB, in resource rich settings. Although LAmB is an advance in overcoming challenges of toxicity and penetration, the expense and need for intravenous treatment remains an issue. In resource limited settings as also in the current situation, where LAmB is scarcely available, clinicians have to re-learn the best ways to use AmB deoxycholate and certain other products about which adequate data is hard to find.

Better outcomes is of course an unmet clinical need and the question arises whether the new Azoles can meet expectations as initial or step-down treatment for mucormycosis. Some Mucorales species have high minimum inhibitory concentrations (MICs) to AmB or to the newer Azoles indicating a degree of intrinsic resistance. AmB is definitely not a drug of choice for Aspergillus which appears as a co-infection in some patients. Additionally, the penetration of AmB into certain sites eg CNS is suboptimal. The inability to have intravenous (IV) to oral switch, toxicity, cost and prolonged duration of treatment are other shortcomings.

Isavuconazole has a labelled indication for Mucormycosis on the basis of the VITAL trial.⁷ However it involved relatively small number of patients, was a single arm, open label

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study with case-control analysis from the Fungiscope registry. The SECURE trial was a phase 3 non-inferiority study of Isavuconazole for Aspergillus and other filamentous fungi. A published post hoc subgroup analysis showed that the mortality in this study was heavily dependent upon recovery of neutropenia.8

Isavuconazole MICs are two times higher than Posaconazole MICs and 4 times higher than AmB MICs but has better bioavailability and plasma exposures which may compensate for the higher MICs and explain clinical efficacy.9 While there is no current recommendation for routine TDM, it may be needed in the real world as additional experience is gathered with this drug.

Posaconazole has not been adequately studied as treatment for mucormycosis. Although the serum levels of Posaconazole are low, the tissue levels are 40 fold.10 High concentrations at the site of infection could increase its efficacy beyond that predicted from serum levels. However, highly variable serum levels were found in critically ill patients even with IV use.11 A small study of IV posaconazole dosing found acceptable but somewhat inconsistent early levels and proposed two daily IV doses for the initial two days rather than for only one day, for the treatment of Mucormycosis.12 The MoveOn study13 was a matched-paired analysis of standard treatment versus new formulations of posaconazole and found encouraging results, although inconsistencies early levels and proposed a combination. If indeed there is a benefit of combination, it would be best realized in patients at the highest risk of poor outcome. However in order to demonstrate superiority, a very large randomized trial is needed. This could have been done in this epidemic, which seems to be a lost opportunity. The role of the second drug may not be for synergy, but can be viewed as that of a supporting drug due to interruptions in AmB therapy caused by various factors including toxicity, cost and erratic availability.

Given the stark realities of drug treatment in the current state, the role of surgery and adequate debridement assumes even more importance. Adjunct therapy with Caspofungin, hyperbaric oxygen, statins, aspirin and deferasirox also needs to be considered more seriously. However there are issues of expense, availability, uncertain efficacy and toxicity with these agents.

The question of prophylaxis for Mucormycosis often comes up considering the large number of cases seen at tertiary care hospitals. However, this is most likely a referral bias as the denominator is unknown. We do not think routine prophylaxis is advisable at this stage. This is based on our unpublished observation of low incidence (about 0.5 to 1%) of mucormycosis developing in COVID-19 cases that were admitted to hospitals where we work. For perspective, prophylaxis for mould infections is recommended for certain groups of hematology-malignancy patients in whom the incidence is about 6%.17 The lack of sufficient supplies of these drugs also have to be factored in while deciding about offering prophylaxis. It may be far more important to emphasize discretion in the use of steroids, and monitoring and treating hyperglycemia as preventive strategies.

In conclusion CAM appears to be a consequence of misinformation, nonchalance and uncontrolled access to drugs used to treat COVID-19, especially steroids. Emphasis on awareness of early warning signs in both patients and care givers is important. Multicentre randomized studies are urgently needed to overcome the myriad uncertainties in managing this difficult mould infection.

References

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