Intercepting the deadly trinity of mucormycosis, diabetes and COVID-19 in India

Of late, several cases of COVID-19-associated mucormycosis (CAM) are being reported worldwide. Although a causal link between COVID-19 and mucormycosis remains unearthed, multiple factors including glucocorticoids, worsening blood glucose control, ketoacidosis, increased serum-free iron (due to hyperferritinemia and acidosis), and viral-induced lymphopenia have been implicated in the pathogenesis of CAM.1

Notably, most of the cases of CAM have been reported from India.2 India, per se, has the highest burden of mucormycosis globally, with an estimated prevalence of 140 cases per million population. Besides, India is home to nearly 77 million people with diabetes; unarguably, diabetes mellitus is a major risk factor for mucormycosis.3 Nevertheless, there has been an unprecedented and alarming upsurge in the number of cases of CAM across several states, as the second wave of the COVID-19 pandemic continues to rampage in India. Until 19 May 2021, approximately 5500 people were affected with CAM in India, resulting in 126 casualties.4 Subsequently, CAM has been declared an epidemic disease in many states across the country.

Amid this raging cataclysm, it is crucial to reflect on the possible reasons and ways to tide over the additional crisis of the ‘black fungus’. As always, prevention is better than cure. Mucorales are ubiquitous organisms, so adopting certain precautions can help curb the magnitude of the CAM epidemic (box 1). First, the huge number of moderate-to-severe COVID-19 cases in the second wave saw an unforeseen use of ‘industrial oxygen’ to address the lack of oxygen supply chain for medical use. Therefore, proper sanitization and handling of oxygen gas cylinders before hospital/home use is of utmost importance.

Second, the role of the hospital environment as point source also needs to be addressed to allow timely and successful implementation of infection control measures. Fungal pathogens are able to persist in bed bars and headers, bedside table, taps and several hospital surfaces from hours to months. Accordingly, adopting simple handwashing measures by healthcare workers and decontaminating high-contact hospital surfaces need to be emphasised. Third, reusable oxygen humidifiers may also play a major role in the transmission of potential nosocomial pathogens via the generation of aerosol particles, for they reach deep into the lung immediately after inhalation.5 In the absence of disposable oxygen humidifiers that carry minimal risk of nosocomial infections, care should be taken for appropriate maintenance of reusable ones. Besides, clean distilled water should be used in humidifiers during oxygen therapy in COVID-19 patients. Fourth, glucocorticoid-induced immunosuppression, hyperglycaemic and lymphopenia predispose to the pathogenesis of mucormycosis. Injudicious use of glucocorticoids in COVID-19 cases without hypoxemia or the utilisation of higher doses of glucocorticoids should be avoided whenever possible. Ketonemia and ketoacidosis have been observed in patients with COVID-19, even in the absence of diabetes mellitus.6 Acidosis can impair phagocytic activity and cause an increase in serum-free iron via proton-mediated displacement of ferric iron from transferrin, leading to the growth of this fungal pathogen.7 Similarly, the rampant use of multivitamins containing zinc and iron as ‘immunity boosters’ that can lead to increased free-iron levels should not be encouraged.

Fifth, voriconazole, often used as antifungal prophylaxis to prevent opportunistic systemic fungal infections, is ineffective against Mucorales and can be responsible for breakthrough mucormycosis infections.8 Likewise, the irrational use of broad-spectrum antibiotics in patients with COVID-19 can also increase the risk of acquiring mucormycosis and should be discouraged.

Lastly, a high index of clinical suspicion for mucormycosis should be kept, not only in patients being treated for COVID-19 but also in those who have recovered from the viral infection. In this regard, mucormycosis cases have been described as late as 42 days and 90 days following COVID-19.9 Individuals who have recently recuperated from COVID-19 should ensure stringent personal hygiene. Post COVID, individuals should be housed in a well-ventilated rather than in a damp environment. They should stay away from decaying organic matters. Visit to dusty places such as construction sites should be avoided.

People requiring oxygen support at home should ensure the use of clean distilled water in oxygen concentrators. Overzealous use of steam inhalation, as well as non-humidified oxygen, can lead to damage of the respiratory mucosa, allowing easy penetration of the Mucorales, hence, it should be limited in post-COVID individuals. Continued use of facemasks would reduce the chances of reinfection with SARS-CoV-2 and minimise the risk of inhalation of fungal spores. However, reusing the same masks for 2–3 weeks may increase the risk of acquiring mucormycosis. Optimum glycaemic control in people with preexisting or new-onset diabetes mellitus should be ensured. At the time of hospital discharge following recovery from COVID-19, individuals should be educated about the early signs and symptoms of mucormycosis and encouraged to seek medical advice at the earliest.

### Box 1: Summarising the possible means of prevention of COVID-19-associated mucormycosis.

- Proper sanitization and handling of oxygen gas cylinders.
- Proper decontamination of hospital environment.
- Use of disposable oxygen humidifiers.
- Use of clean distilled water in oxygen humidifiers and oxygen concentrators.
- Use of glucocorticoids for the management of COVID-19 at the lowest possible dose and for the limited possible duration.
- Avoidance of use of iron and zinc supplements for the management of COVID-19.
- Avoidance of use of voriconazole as an antifungal prophylaxis.
- Avoidance of use of broad-spectrum antibiotics, unless indicated.
- Strict maintenance of personal hygiene even after recovery from COVID-19.
- Avoid living in a damp environment.
- Avoid overzealous use of steam inhalation and non-humidified oxygen.
- Maintenance of good glycaemic control in people with diabetes mellitus.
- Educating people with COVID-19 about the early signs and symptoms of mucormycosis at the time of hospital discharge.
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