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Letters to the editor

Mucormycosis in COVID-19: The Indian scenario

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Sir,—Mucormycosis is the latest addition to the growing woes of Indians since the inception of COVID-19. The past months have seen a remarkable increase in the incidence of this dreadful disease. We want to highlight a few salient points concerning this phenomenon.

Why the increased incidence in India, despite being a country with infrastructural shortcomings for diagnosis of mucormycosis, especially during this surge of COVID-19?

Although the precise incidence of mucormycosis in India remains unknown, recent studies have unanimously underscored it to be handsomely exceeding that in developed countries. The estimated prevalence of mucormycosis is approximately 70 times higher in India than in the rest of the world [1]. The conceivable reasons underneath are (1) ample abundance of the contagion in both healthcare setups and familiar community places; (2) umpteen number of susceptible hosts (especially patients with uncontrolled/poorly-controlled diabetes, chronic kidney disease and renal transplants, chronic obstructive pulmonary disease, pulmonary tuberculosis, and hematological malignancies); and (3) favorable environment for mucormycosis (tropical/sub-tropical humid climate and poor air and housing quality, especially among people with lower socioeconomic status). It is surprising and frightening that COVID-19 might create an internal milieu that helps these fungi thrive, survive, sprout out, and invade. Muthu et al. [2] perfectly pointed out the micro-environmental backdrops (i.e., hypoxia, hyperglycemia, indiscriminate steroid usage, high ferritin (iron) levels, metabolic acidosis, immunosuppression, prolonged hospital stay, and invasive/non-invasive ventilation) for an out of proportion surge in cases of mucormycosis during the ongoing COVID-19 pandemic. Diabetes mellitus, particularly when uncontrolled, is the most notorious independent risk factor for mucormycosis [2]. Indeed, diabetes mellitus was more frequently reported in COVID-19 associated mucormycosis (CAM) in India (n = 233) compared to the rest of the world (n = 42) (66.1% vs. 54.8%), according to one report [2]. The presentation of CAM was also significantly different, with rhino-orbital and rhino-orbito-cerebral mucormycosis being the most frequently encountered in Indian patients compared to pulmonary and disseminated varieties globally (89% vs. 64%, p = 0.001). However, this difference may be due to inadequate diagnosis and lack of reporting [2].

An observational study from Eastern India on 55 patients noticed that middle-aged, male diabetics were having the highest risk of CAM [3]. They also reported a diverse spectrum related to the neuro-axis burden, where extraocular movements and the optic nerve were most commonly affected [3]. Interestingly, there was also a regional difference in the surge of mucormycosis, which is yet to be explored [3].

Why has there been a surge of "difficult to control" hyperglycemia in the time of COVID-19?

COVID-19, diabetes mellitus, and abnormal glucose excursions have been some of the most studied topics. Apart from the alteration at the cellular level that explains the metabolic disaster (i.e., increased insulin resistance in the backdrop of infection, cytokine storm, beta-cell damage related insulinopenia by the virus, excess production of counter-regulatory hormones, and severe activity restriction during isolation/hospital-stay among others), there are other seemingly primary reasons for this. Firstly, non-adherence to the prescribed anti-diabetic regimen is a severe problem in India. Secondly, “therapeutic inertia” (on the part of the patient, physicians, and the healthcare delivery system) always has been a contributing factor, and more so in these times. Third, we should keep in mind the disadvantages of telemedicine because it is challenging to achieve tele-euglycemia without repeated doctor-patient interaction, trial and error, and strict regular monitoring of energy intake and expenditure. Fourth, indigenous medicine practitioners (otherwise known as quacks) also treat diabetes mellitus, even in this age of precision-based medicine; the outcome is anybody's guess [4]. Fifth is the age-old problem of “over-the-counter” availability of almost all the medicines in this country. People with unknown glycemic status hear media propaganda and “infodemic” about steroids being “game-changers” in COVID-19. They get them either by themselves or by illicit prescription from quacks or legit yet imperfect prescriptions from teleconsultations without monitoring adverse events. In the case of hospitalized patients, the picture is a bit different but dire. Causes of “difficult to control” glucose excursions in patients are again due to “therapeutic inertia” on the part of the treating physicians (time crunches, lack of consensus guidelines for COVID-19 related diabetes, reluctance to start and intensify insulin therapy in fear of precipitation of hypoglycemia, a continuation of metformin in hypoxic patients, and that many doctors who are specialists in subjects other than endocrinology have been required to manage such patients as front-liners because of crisis). In addition, “therapeutic inertia” is due to the faulty healthcare system (lack of continuous supply of oral anti-diabetics and insulin inwards, lack of supervised, integrated, holistic team-based care and poverty of healthcare plans,

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inadequate pro-active approach, and no insurance coverage for expenses in most occasions).

Increased incidence in India compared to other countries

Indeed, the incidence of mucormycosis is higher in India than in other countries; several other macro-environmental factors might be contributing to this: Ryle's tube, Foley catheter, and nebulization masks are not properly discarded. The reusable instruments are not properly sterilized or autoclaved. The central air conditioning systems in many hospitals are breeding grounds for fungi. This, combined with a lack of cross-ventilation and humid weather, is ideal for fungal infections.

Rampant, unsupervised use of corticosteroids

The use of corticosteroids has become ubiquitous. They are used rampantly in greater than needed dosage, for a longer duration, without monitoring for adverse events and co-morbidities, and sometimes, even for mildest disease. Now, why is this occurring and more so in India? Firstly, glucocorticoids have been the only drug apart from anticoagulants and supplemental oxygen, which decrease disease severity and mortality. Hence it has been widely recommended for all patients with moderate to severe disease. However, due to the lack of consensus amidst several guidelines, physicians are compelled to treat patients with an individualistic approach without supervised guidance from academically superior authorities. Secondly, ubiquitous quack practice and telemedicine have their role in this outbreak of the use of corticosteroids and their ill effects. Finally, “uneducated” and irresponsible propaganda by mass media to promote steroids as a “game-changer” in the first few months and then again as a “villain” after the advent of these mucormycosis cases.

Is the widespread use of zinc supplements to blame?

Zinc, an essential nutrient for many fungi, including Mucorales, has been in routine use as part of the treatment regimen in COVID-19. Zinc directly regulates the fungal proteins necessary to infect the mammalian hosts. Our immune system usually defends against a fungal invasion by “hiding” the zinc, providing us with a sort of “nutritional immunity” [1]. A recent *in vitro* study on eight isolates of *Rhizopus arrhizus* from CAM patients revealed a visible increase in growth with Zinc enrichment [5]. Therefore, increased use of zinc supplements may be a scenario worth looking into. Again, indigenous medicine practitioners, tele consultants, and even many certified physicians have to introspect why they ran after zinc and multivitamins when there was no robust evidence.

Role of iron

Much like Zinc, iron acquisition from the host is also a key mechanism for the growth of Mucorales, as evident from *in vitro* studies [2]. On the one hand, patients with iron overload receiving deferoxamine are more prone to mucormycosis. On the other hand, COVID-19 induces an hyper-inflammatory state causing hyperferritinemia, which affects both innate and adaptive immunity, making the patients vulnerable to fungal infections [2].

Industrial oxygen: a crisis-curtailer or the havoc-harbinger?

The risk of microbial infections from reusable oxygen humidifiers is well known. A recent systematic analysis of 12 studies across the globe revealed that reusing humidifiers without following proper aseptic protocols could increase the risk of contamination [6]. Jadhav et al. [7] showed that a high percentage of samples taken from oxygen humidifiers and Hudson's chambers of nebulizers had fungal colonization, which was more in reusable humidifiers, pointing to a high risk of nosocomial infections. Moulds frequently contaminate nebulizers, and proper care should be taken to maintain nebulizer hygiene.

Role of antifungal prophylaxis and voriconazole, and the rampant use of antibiotics

Like immunosuppressant drugs, the increased risk of mucormycosis can be attributed to prophylactic or pre-emptive antifungal therapy. For example, in animal models, voriconazole pre-exposure may select for breakthrough mucormycosis [8]. Moreover, antibiotics such as azithromycin and hydroxychloroquine have been used inappropriately since the inception of COVID-19 in India. A delicate natural balance exists between the microbiome and the mycobiome in the nasal and respiratory epithelium [9]. Thus, rampant over-the-counter antibiotics, some of which have been marketed as “miracle cures” without any substantial evidence, only add to the growing problem and make the patients vulnerable to fungal infections.

Role of tocilizumab

Immunomodulatory therapy has been tried extensively in COVID-19 to combat the hyper-inflammatory systemic response. One mainstay of this therapy, tocilizumab, is a known cause of increased bacterial and soft tissue infections [10].

In order to prevent future outbreaks of mucormycosis in India during this pandemic, we suggest that several preventive measures should be implemented. First, strict maintenance of hygiene in and around hospital wards and premises. Further, hospitals should regularly test fungus from air conditioners, oxygen cylinders, and humidifiers. Second, steroid usage should be optimal and only when indicated. Third, strict glucose monitoring and hyperglycemia control. Fourth, we have to notice early signs and symptoms such as a blocked nose or abnormal discharge. Finally, we should curb the use of antimicrobial and antifungal prophylaxis.

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