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COVID 19 and Mucormycosis Co-infection

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Coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS CoV 2) has been associated with a wide range of opportunistic infections due to bacteria and fungi.[1] Opportunistic fungal pathogens in COVID-19 patients, namely, *Aspergillus* and *Candida* were reported earlier.[2] In the recent past, many cases of Mucormycosis and COVID-19 co-infection were reported in literatures.[1]

Several reasons behind the increasing occurrence of such co-morbidities were advocated. The first and the foremost condition allowing an opportunistic infection like Mucormycosis to get established is an immunocompromised state of the host.[3] However, there are limited clues to find any causal relationship between COVID-19 and superadded infection due to the opportunistic fungi belonging to the order *Mucoreles*. Various views have nevertheless, been laid out.

Firstly, it is true that many of us prefer administering steroids to COVID-19 patients to tackle the uncontrolled pro-inflammatory event, and to avoid the deleterious effect of the cytokine storm, invariably seen among these individuals. Steroids behave as double-edged swords. While minimizing the proinflammatory host response, these agents simultaneously enhance immunosuppression, and can also deteriorate the glycemic control in the diabetic patients co-infected with the COVID-19 virus.[4]

Comorbid conditions like diabetes mellitus in a COVID-19 patient may induce certain additional host environmental changes which could facilitate the growth and multiplication of *Muco*r and the related fungi belonging to the *Mucorales* group. As the majority of COVID-19 patients are hypoxic and may be hyperglycemic due to associated diabetes, spores of *Muco*r and other related fungi take advantage of both these host conditions to germinate, giving rise to the hyphal forms which are known to cause tissue invasion, especially invasion of the blood vessels.

Secondly, the increase in serum ferritin levels, among COVID-19 patients is an additional contributing factor for the survival and multiplication of the fungi. Members of the *Mucorales* order, i.e. Mucor, Rhizopus, Rhizomucor, Absidia, Cunnighamella, Apophysomyces, possess high-affinity surface receptor molecules which can absorb ferritin from the host micro-environment.[5]

Thirdly, the decreased phagocytic activity of the white blood cells arising as a result of uncontrolled diabetes and steroid mediated immunosuppression, could accelerate the spread of the fungi as well.

Such rapid spread and invasion by the fungus give rise to various clinical forms of mucormycosis of which the Rhinocerebral or the Rhino-sino-orbito cerebral variety happens to be the most life-threatening condition because of the easy dissemination of the infected emboli from the paranasal sinus and orbital areas to the brain by contiguous or retrograde hematogenous spread.[6,7]

Considering the aforementioned facts regarding the severity of the clinical condition

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arising out of this comorbidity, timely and appropriate management of mucormycosis remains the key element to save the life of the patient. It can be reiterated here that the majority of COVID-19 patients come back with signs and symptoms of mucormycosis in about 14-18 days after getting discharged from the hospital.[8] It should be a requirement, therefore, on the part of the treating physician to counsel the patient on discharge about the initial milder features of mucormycosis; such as facial pain and swelling, headache, fever, nasal blockage, and brown colored nasal discharge; such that the patient is aware of these presentations, and the time when he/she self-scrutinizes these features, he/she may immediately seek medical attention. After examining the patient, a suitable biopsied material from the sinus cavity, collected in sterile normal saline should be sent to the laboratory. Any good clinical diagnostic laboratory should be able to give the diagnosis in an hour, which will help in initiating the antifungal therapy.

Besides antifungal therapy, the prime management of COVID-19 and mucormycosis co-infection encompasses glycemic control, if the patient is diabetic, reduction of the dosage, or even omission of steroids, if possible. In addition, surgical removal of necrotic material from the paranasal sinus cavities is all the more important, keeping in view the rapid healing process and better drug penetration. [9]

Administration of antifungal agents is as important as the surgery. The choicest antifungal drug is liposomal amphotericin B which is effective both against *Mucor* and *Aspergillus* infections.[10] This can be administered safely in a high dosage of 5-10 mg/kg/day intravenously.[10]

The only drawback of this drug is its high cost, making it unaffordable for patients belonging to low-income groups, as well as its frequent unavailability even in the tertiary care hospitals in many developing countries. On the other hand, amphotericin B deoxycholate is cheaper and is readily available. However it is nephrotoxic, and so is administered at a lower dose i.e. 1-1.5 mg/kg/day via slow intravenous infusion with 5% dextrose solution.[10] Despite that, constant monitoring of renal parameters is important while the patient is on amphotericin B deoxycholate.

After clinical improvement either with liposomal amphotericin B or amphotericin B deoxycholate, the intravenous regime is discontinued and the patient is kept on oral antifungal drugs like isavuconazole 200 mg QID for a period of another 3-4 months. It is worthwhile to clarify at this point that drugs such as fluconazole, voriconazole, or echinocandins are ineffective against mucormycosis.

Lastly, it will be appropriate to mention here a bottom-line truth about the causative agent i.e.Mucor/Rhizopus. To name this microorganism as "black fungus' is a misnomer. *Mucor* species have recently been called "black fungi" by certain sectors, probably because of the dark brown lesions seen in mucormycosis of the nose, paranasal sinuses, and hard palate. This happens due to the angioinvasive nature of the fungus and subsequent erosion of blood vessels. It does not produce any black pigment either in *in vivo* situations or on culture. On the contrary, the term "black fungi" applies to a distinct entity of fungi, collectively known as dematiaceous fungi, which have the inherent property of producing black pigment. The dematiaceous group comprises of the genera, *Curvularia, Alternaria, Bipolaris, Helminthosporium*, which are soil saprophytes, and are well known to cause fungal keratitis mostly in people who are farmers or agricultural workers by occupation and may acquire corneal infection due to accidental trauma to the eye with vegetative matter or soil.

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