Rhino-orbital mucormycosis related to COVID-19- A case series exploring risk factors

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Case Report

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Abstract

There has been a surge of rhino-orbital mucormycosis cases in India in the wake of the second wave of the COVID-19 pandemic. It has been widely suggested that dysglycaemia due to diabetes present as a common comorbidity in these COVID-19 patients as well as indiscriminate steroid use has resulted in this surge. Here, we report a series of 13 cases of rhino-orbital mucormycosis in COVID-19 patients admitted at our center between mid-April and early June 2021. Out of the 13, the only common factor was COVID-19 at some time point before diagnosis of mucormycosis or coexistent with it. The cases showed a male preponderance and four of them showed intracranial extension of disease. Eleven of them had received steroids as part of COVID-19 management protocol and twelve of them had pre-existing or newly diagnosed diabetes. We have summarized other probable risk factors being considered such as immunosuppressed state, antiviral and Ayurvedic (Indian traditional) medications, oxygen therapy, with each of which we could not find a link of mucormycosis. We propose that COVID-19 itself through molecular mechanisms predisposes to mucormycosis, with other factors such as dysglycaemia providing a second hit.

Introduction

The second wave of COVID-19 in India has seen an unprecedented surge of mucormycosis cases in its wake, with more than 14000 cases occurring countrywide. [1] Mucormycosis is a highly invasive infection caused by fungi of the order Mucorales (*Rhizopus* sp., *Apophysomyces* sp., *Lichtheimia* sp., *Mucor* sp. etc), most commonly involving the para-nasal sinuses and orbit with probable intracranial extension. The mortality of mucormycosis is more than 50% even with treatment, and morbidity in the form of loss of vision is also extremely high. [2, 3] The exact cause of the increase in mucormycosis cases following COVID-19 is unclear. It has been suggested that COVID-19 patients with diabetes, which is already the leading risk factor for mucormycosis, may have been administered irrational doses of steroids for prolonged periods as a part of COVID-19 management algorithm, and the ensuing dysglycaemia may have triggered the mucormycosis epidemic. Here, we present a series of cases of rhino-orbital mucormycosis and infer the possible risk factors for this fungal epidemic.

Case Series

We report here the case details of 13 patients of rhino-orbital mucormycosis admitted between mid-April to early June 2021 who provided written informed consent for reporting their cases. The mean age of our patients (10 males, 3 females) was 51.5 years (std.dev.10.3 years). Except for one patient, all had history of diabetes mellitus or were newly diagnosed to have diabetes at the time of presentation for mucormycosis, but none of the patients had evidence of diabetic ketoacidosis. Each patient barring one had tested positive for SARS-CoV-2 on RT-PCR performed on nasal/oropharyngeal swab sample. The single patient who was RT-PCR negative had high resolution computed tomography (HRCT) imaging features of the lungs, highly suggestive for COVID-19 disease. Four patients were detected to be RT-PCR positive after developing symptoms of mucormycosis. It may be presumed that these patients either had

mild or asymptomatic COVID or voluntarily did not get tested for COVID till they presented with bothersome mucormycosis symptoms. One of these patients had mucormycosis symptoms for almost a month before testing RT-PCR positive for SARS-CoV-2. Prolonged viral shedding may be a possibility in this patient in line with new evidence in immunocompromised patients. However, none of the patients were positive for HIV, though 11 out of the 13 patients had received steroids as part of COVID management protocol. Rationality of steroid treatment in each could not be ascertained. In several cases, steroids had been initiated before presentation to our hospital. Four patients had intracranial manifestations of disease. The demographic and clinical profile of the patients are detailed in **Table 1**.

Potassium hydroxide (KOH) wet mount and fungal culture/sensitivity were done from nasal swab pre-operatively and from tissue sample obtained during operative intervention. Histopathological examination of tissue sample was also performed. Diagnosis of mucormycosis was based on typical clinical presentation supported by positive results in any of these investigations, except in three patients where CT imaging findings were suggestive, but tissue diagnosis/culture reports are awaited. Each patient received amphotericin B/posaconazole based on national guidelines. The surgical management for each patient is detailed in **Table 1**. Outcomes are not elaborated as follow-up observation period has not been adequate as yet. There has however been no mortality in this group.

Discussion

The reasons behind the upsurge of mucormycosis cases in India are still unclear. Several factors including use of steroids and other immunomodulators such as tocilizumab, anti-virals, ayurvedic (traditional Indian) medicines especially oils to be instilled in the nose, iron overuse, and use of industrial oxygen have been suggested to play a part. A look at **Table 1** however suggests that none of these factors, including steroids and diabetes were uniformly present in the COVID-19 patients presenting with rhino-orbital mucormycosis. Only six out of 13 patients had received oxygen at some point, none had received iron recently, and only one patient had been taking ayurvedic oral medicines (containing Ashwagandha, *Withania somnifera*). It is quite likely that any of the studied factors such as dysglycaemia might have played only a facilitatory role in triggering mucormycosis cases. We may conclude that COVID-19 has been the primary risk factor for invasive fungal disease. COVID-19 has been observed to increase serum concentrations of GRP78, a heat-shock protein involved in stress-responses. [4] GRP78 has been demonstrated to bind to *Rhizopus* germlings, which are the major invading forms of Mucorales. [5] Further, antibodies directed against GRP78 and short hairpin RNA (shRNA) sequences targeting GRP78 have been observed to suppress invasion and endothelial damage induced by *Rhizopus delemar* but not by other pathogenic fungi such as *Candida* and *Aspergillus*. [5, 6] Interestingly, anti-GRP78 antibodies have been suggested as potential COVID-19 therapeutic options. [7] This may have a dual effect and may reduce risk of mucormycosis too. A second link between COVID-19 and mucormycosis involves the spleen tyrosine kinase, an enzyme involved in phagocytic function of neutrophils, macrophages etc, and hence playing a major role in anti-fungal defense. Urine proteome analysis of COVID-19 patients has shown a down-regulation of spleen-tyrosine kinase, which may impair phagocytosis and predispose to invasive mucormycosis. [8] Paradoxically, Fostamatinib, a small

molecule inhibitor of spleen tyrosine kinase, is being tested in clinical trials of COVID-19 patients to improve outcomes by inhibiting pro-inflammatory cytokines and the neutrophil extracellular trap. [9] In contrast to therapies targeting GRP78, this drug may prove to increase the risk of invasive mucormycosis, by inhibiting the phagocytic anti-fungal defense of the body. The interplay of COVID-19 and mucormycosis needs to be worked out based on these pathogenetic pathways in order to adequately prevent the invasive fungal disease with high mortality.

Declarations

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Consent to publish: Written informed consent taken from each patient or from legal guardian for patients unable to provide consent.

Ethical statement: No human/animal experimentation was performed. Only standard medical/surgical care was provided, and written informed consent taken from each patient/legal guardian to publish. Institute Ethical Committee approval obtained.

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Tables

Due to technical limitations, table 1 is only available as a download in the supplementary files section.

Supplementary Files

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- [table1.pdf](#)