



## COVID ASSOCIATED MUCORMYCOSIS — A MULTIDISCIPLINARY APPROACH

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**ABSTRACT** Mucormycosis is an aggressive, angioinvasive fungal infection, acquired via inhalation of environmental spores or by inoculation affecting severely immunocompromised hosts caused by fungal species belonging to order Mucorales. Invasive Mucormycosis (IM) has been increasingly documented in patients with coronavirus disease 2019 (COVID-19). Predisposing factors include diabetes, steroid use, neutropenia, malignancies, and immunocompromised individuals. COVID-19 associated rhino-orbital-cerebral mucormycosis (ROCM) has reached epidemic proportion during India's second wave of COVID-19 pandemic caused due to  $\delta$ -variant, with several risk factors being implicated in its pathogenesis. This study is a case series of thirty cases of Covid Associated Mucormycosis (CAM) aimed to determine the patient demographics, risk factors including co-morbidities, and medications used to treat COVID-19, presenting symptoms and signs, and the outcome of management.

**KEYWORDS :** COVID-19, rhino-orbital-cerebral mucormycosis, immunosuppression, endoscopic sinus debridement, RT-PCR.

### METHODS:

This was a retrospective, observational study of thirty patients with COVID-19-associated ROCM from May 2021 to July 2021. The diagnosis of COVID-19 was based on reverse transcription polymerase chain reaction (RT-PCR) test on nasopharyngeal or oropharyngeal swabs to be positive in a clinically symptomatic case. A patient with symptoms and signs of ROCM, in the clinical setting of concurrent or recently treated COVID-19, was considered as possible ROCM. If clinical features were supported by diagnostic nasal endoscopy findings, contrast-enhanced magnetic resonance imaging (MRI), or CT scan, probable ROCM was diagnosed. Proven ROCM was defined as clinico-radiological features along with microbiological confirmation on direct microscopy and/or culture or histopathology with special stains or molecular diagnostics. Patients with non-COVID-19-associated ROCM or those with proven non-mucor fungal infections were excluded from the study. A working staging system has been proposed to help triage these patients and customize their care. The system is simple and follows the general anatomical progression of ROCM from the point of entry (nasal mucosa) on to the paranasal sinus (PNS), orbit, and central nervous system (CNS), and severity in each of these anatomical locations. In this study, all the patients were retrospectively classified into the proposed staging system. The data was analyzed using Microsoft Excel.

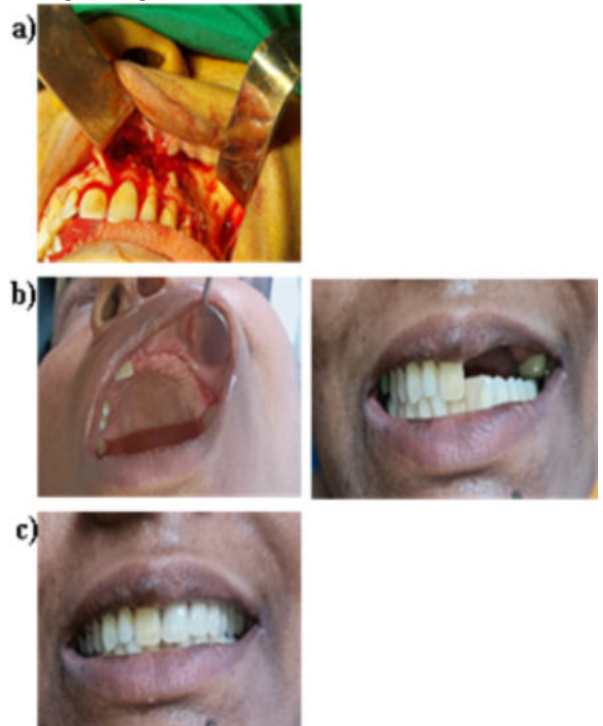
### Case 1

35-year-old post covid female, newly detected diabetes mellitus had left side loosening of tooth (Figure 1 & 2) with dental pain for past 15 days. On examination, left gingival abscess in 21 to 25. On nasal endoscopy, mucopurulent discharge in left middle meatus. Nasal sensation was found to be decreased. Gingival abscess swab for KOH mount showed broad aseptate hyphae suggestive of Mucormycosis. Partial maxillectomy with endoscopic sinus debridement was performed.

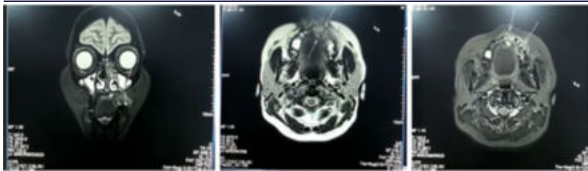
### Case 2

55-year-old post covid female, newly detected diabetes mellitus had right side facial pain with diplopia for past 10 days. On examination, right eye lateral gaze restricted with mild proptosis & no chemosis. On

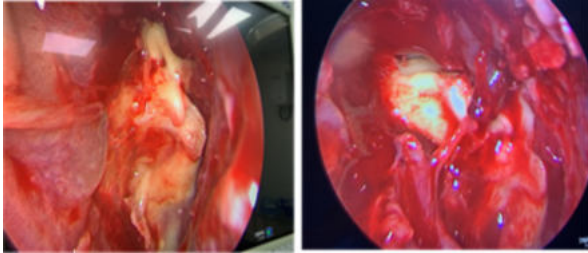
nasal endoscopy (Figure 3 & 4), mucopurulent discharge in right middle meatus and nasal sensation was decreased. Nasal swab for KOH mount revealed broad aseptate hyphae suggestive of Mucormycosis. Endoscopic sinus debridement with orbital decompression procedure was carried out.



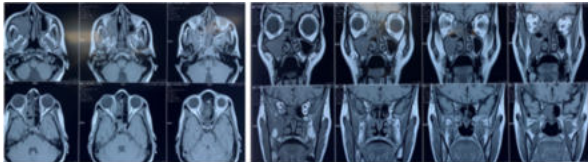
**Figure 1.** a) Intra operative image showing disease involving and eroding alveolus; b) Post operative image; c) post operative after fitting with artificial dental prosthesis.



**Figure 2.** Bony erosions involving the maxillary alveolus & hard palate on the left side with marrow edema & adjacent soft tissue edema



**Figure 3.** a) Intra op endoscopic picture showing mucopurulent disease in ethmoidal region on the right side. b) Intra op endoscopic picture showing mucopurulent disease in the intra orbital part of extra conal space.

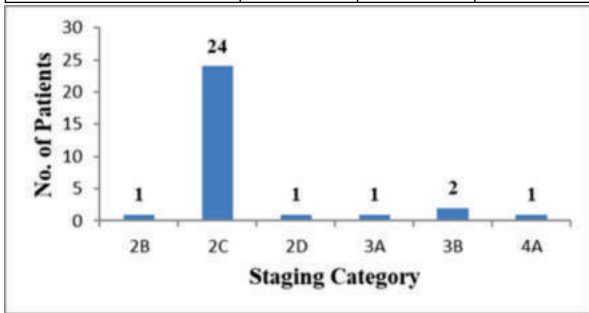


**Figure 4.** Sinonasal disease seen completely filling the right maxillary, ethmoid & sphenoid sinus with infiltrations to involve medial rectal muscle & extra conal space of orbit.

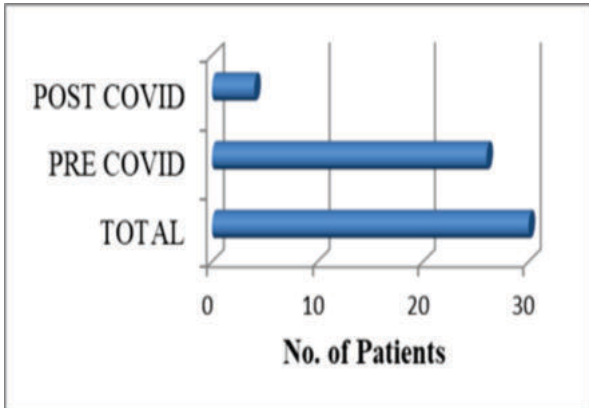
**RESULTS:**

**Table 1. Age Wise Distribution Of 30 Patients**

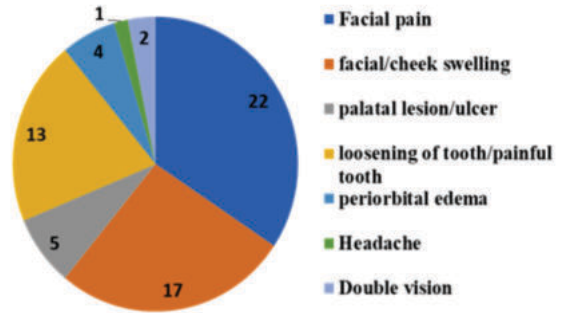
S.No	Age Groups	Male	Female	Total
1	31-40	6	2	8
2	41-50	7	3	10
3	51-60	3	5	8
4	61-70	2	1	3
5	71-80	1	-	1
Total		19	11	30



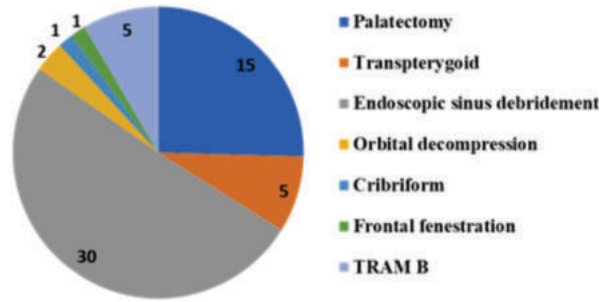
**Figure 5.** Staging category of 30 patients.



**Figure 6.** Status Of Diabetic Condition During Covid Infection In The Study Population.



**Figure 7.** Frequency Of Primary Symptoms In Patients With COVID-19-Associated Rhino-orbital-cerebral Mucormycosis.

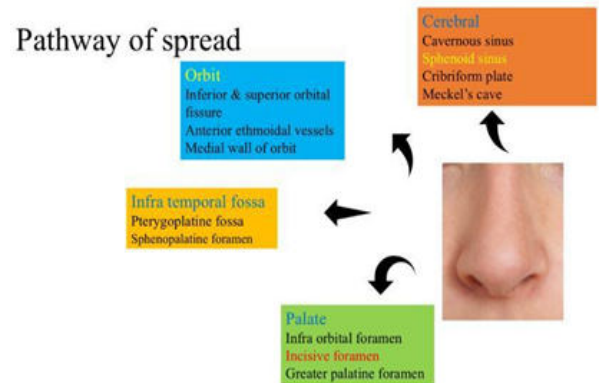


**Figure 8.** Surgical Procedure Followed For The Patients.

**DISCUSSION**

Invasive Mucormycosis (IM) is a life-threatening infection caused by order Mucorales. It is an opportunistic fungal infection caused by saprophytic aerobic fungi which is acquired via the inhalation of spores into the paranasal sinuses of the host. Mucormycosis in COVID-19 patients has become an important concern. The clinical presentation of IM is Rhino-orbital-cerebral mucormycosis (ROCM) often occurs in immunocompromised individuals. In India, this COVID-19 associated ROCM were increased exponentially during the second wave of COVID-19. We retrospectively, observed 30 patients with COVID-19-associated ROCM. The mean age of 30 patients affected was 48.5 (30-75years), in which, patients in the age group of 50-59 years were most common.

ROCM can be categorised into different stages based on the severity of disease. This depends on the dissemination of disease from the point of entry (nasal) to CNS (central nervous system).



**Figure 9.** Pathway Of Spread Of Mucormycosis From Nose To Adjacent Areas.

In this study, 26 patients were in Stage 2, 3 patients were in Stage 3 and 1 patient were in stage 4. This staging distribution of the patients is achieved by their signs, symptoms and it was preliminarily diagnosed by endoscopy, MRI or CT scan. Later it was further confirmed by microbiology, histopathology and molecular diagnostics of their samples. The rise of ROCM in patients with COVID-19 is due to underlying comorbidities such as diabetes mellitus (DM), malignancies, steroids and immunosuppressant medications. Pre-existing DM is the major risk factor that spreads the fungal infection.

India is the second-highest number of adults (20-79 years) living with diabetes. However, patients with diabetes are 7.5 times more likely to develop mucormycosis<sup>1</sup>. Many recent studies observed the new onset of diabetes in post COVID-19 patients. In our study, 26 (86%) patients were found to have DM before COVID-19 infection, whereas 4 (14%) patients developed diabetes in post COVID-19. In a case study of 41 patients with COVID-19 associated mucormycosis, 94% were diabetic<sup>2</sup>.

Extensive use of steam inhalation with high temperature may cause the individual vulnerable to mucormycosis who is already immune depleted with covid infection. This is due to the damage of nasal mucosa which leads to invasive fungal infection. In our study, 80% of study population were found to have a history of steam inhalation and 20% had no history of steam inhalation. This observation was comparable with the previous study, in which 84.1% of the case group had a practise of steam inhalation<sup>3</sup>.

ROCM occurs in association with active COVID-19 infection as well as post recovery. In a case study of 80 ROCM patients, 93% were hospitalised with COVID-19 infection<sup>4</sup>. Of 2826 cases from different states of India, 44% of patients had delayed onset of ROCM beyond 14 days after COVID-19<sup>5</sup>. In our study, 26 (86%) patients developed mucormycosis in post covid and 4 (14%) patients developed mucormycosis during the active phase of covid infection.

The main stay in the management of mucormycosis is surgical debridement followed by antifungal therapy and management of DM. The surgical management depends upon the extent of involvement/staging of disease. In all the cases, endoscopic approach was performed for disease clearance, in one case (frontal sinus involvement case) alone combined endoscopic and external approach was performed. The frontal fenestration approached externally due to proximity of disease to the lateral aspect of frontal sinus. Intricate anatomy of sinuses demands the need of the endoscopic approach to clear off the disease. All the foramina need to be cleared to prevent extension of disease to adjacent structure and to avoid revision surgery. Pneumatisation of sphenoid sinus plays a major role in spread of disease. In a well pneumatized sphenoid sinus, disease in the lateral recess have an easy way to spread to cavernous sinus or middle cranial fossa. Hence adequate endoscopic sinus debridement needed in these cases.

In case of a disease involving the palate, palatotomy was performed. After ensuring healing of the cavity, obturator prosthesis was delivered to the patient. Another challenge in the management of mucormycosis was the shortage of Amphotericin B and even when it was available it needs to be diluted in 5% dextrose, hence the diabetic management in addition to that monitoring for nephrotoxicity and dyselektrolytemia during amphotericin B became crucial to the treatment of CAM. Following Amphotericin, most patients were maintained on oral Posaconazole.

Diagnosis of COVID-19-associated mucormycosis is achieved by direct mycological and histological examinations which is a gold standard technique. Microbiological culture is required for identification of genus, species, and antifungal susceptibility. *Rhizopus* sp were the most common species identified in 19 (32%) of 59 patients with rhino-orbital cerebral infection and 15 (71%) of 21 patients with pulmonary, gastrointestinal, or disseminated disease. *Mucor* sp were identified only in patients with rhino-orbital cerebral disease (six of 59 patients)<sup>1</sup>. In our study, upon culturing the patient samples, Mucorales were identified in 29 patients and Mucorales along with *Aspergillus* was identified in 1 patient. When compared to histology and culture, PCR is rapid test that can be used on both serum and paraffin-embedded tissue to detect DNA of Mucorales<sup>6</sup>. In this study, ROCM was also diagnosed by real-time PCR using Mucor Genius PCR kit (PN-700) which targets 28S rRNA gene. Other targets include, 28S rDNA, the mitochondrial gene rml, the cytochrome b gene or the Mucorales-specific CoH gene had also been investigated<sup>6</sup>. The combination of 18S and 28S rRNA targeting genes detects all the clinical samples with proven Mucorales infection<sup>7</sup>.

## CONCLUSION

Mucormycosis is an aggressive, angioinvasive fungal infection, acquired via inhalation of environmental spores or by inoculation affecting severely immunocompromised patients. CAM was an epidermic due to the pandemic of COVID-19 in India during the

second wave caused due to  $\delta$ -variant. Early diagnosis and timely intervention by surgical and antifungal therapy improved the outcome of ROCM among covid patients. Caution needs to be exercised regarding the injudicious use of steam inhalation. Stringent glycemic control, avoidance of inadvertent use of steroids can reduce the incidence of Invasive Mucormycosis.

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