



# Post COVID-19 Mucormycosis-The Horizon

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## Abstract

**Objective** Acute Invasive Fungal Rhinosinusitis is a rare condition which recently has gained attention due to its increased occurrence in the post COVID-19 patients past the second wave. The current study retrospectively evaluates the occurrence of Acute Invasive Fungal Rhinosinusitis (Mucormycosis) in post COVID-19 (Corona Virus Disease-19) patients.

**Methods** A descriptive study included patients diagnosed with Acute Invasive Fungal Rhinosinusitis (Mucormycosis) after recent COVID-19 infection. 110 patients were evaluated retrospectively with histopathological confirmation of Mucormycosis. Surgical treatment was restricted to patients who tested Real Time Polymerase Chain Reaction (RT PCR) negative for COVID-19 except for three patients who were tested positive. Antifungal agents were given to patients following surgery.

**Results** A total of 110 patients with a mean age of 48.42 years were included. The most common risk factor was diabetes mellitus (88.2%). Sino-nasal, orbital, palatal and intracranial involvement were 57.9%, 48.5%, 12.7% and 5.6% respectively. Histopathological confirmation revealed mucormycosis. The most common reported symptoms were periorbital oedema (20.5%), headache (20.3%), gingival swelling (18.5%) facial pain (18.4%) and facial swelling (18.2%). All the patients were treated with surgical debridement and antifungal medications. The overall survival rate was 95.32%.

**Conclusion** Acute Invasive Fungal Rhinosinusitis is a life-threatening opportunistic infection. Patients with moderate to severe COVID-19 infection are more susceptible to it. Uncontrolled diabetes mellitus and intake of corticosteroids increase the risk of developing Acute Invasive Fungal Rhinosinusitis. Early diagnosis and timely management can improve survival rates of the patients.

**Keywords** Acute invasive fungal sinusitis · Post COVID-19 · Mucormycosis · Mucoraceae.

## Introduction

Coronavirus disease 2019 (COVID-19), the highly contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the leading cause of emergency global pandemic [1]. COVID-19 patients found to have immunosuppression due to decrease in CD4+(Cluster of differentiation) T cells and CD8 + T cells. This immune suppression resulted in a diverse bacterial and fungal infections in association with comorbidities like diabetes mellitus [2].

Acute Invasive Fungal Rhino sinusitis (AIFRS) is a rare disease with high morbidity and mortality. Acute Invasive

Fungal sinusitis is an aggressive and fatal infection of the paranasal sinuses and neighbouring vital organs. The spread and pathogenesis of the disease is by angioinvasion. The causative pathogens are a diverse group of fungal organisms that are widely distributed within the environment. Normally functioning as saprophytes that inhabit decomposing organic matter, these organisms become pathogenic under the right circumstances. Many fungal species can cause invasive infections, but the Zygomycetes (Rhizopus, Mucor, Rhizomucor) and species of Aspergillus are the most common etiologic agents in the sino-nasal cavity [3].

The presentation of AIFRS can be quite variable therefore clinical suspicion for AIFRS should be raised in the immunocompromised patient (COVID-19 infection in our study) presenting with new onset and rapidly progressive sinusitis or facial discomfort. Nasal endoscopy demonstrates areas of mucosal ischemia, frank necrosis or crusting. Radiographic imaging shows nonspecific findings of sinus opacification. Histopathological confirmation of the diagnosis requires the

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presence of invasive fungal elements within the submucosal tissues of the nasal cavity or paranasal sinuses. Early and accurate diagnosis is essential as the prognosis is governed by the surgical debridement and rapid initiation of antifungal therapy [3].

## Materials and methods

### Study setting

A retrospective descriptive study was being conducted in a tertiary ENT care centre, the nodal centre for mucormycosis.

### Study population

Hundred and ten patients diagnosed with mucormycosis associated with recent COVID-19 infection from May 2021 to June 2021. The diagnosis of mucormycosis was made based on acute onset, rapid progression and histopathological confirmation.

### Inclusion criteria

Patients who were tested Real Time Polymerase Chain Reaction (RT PCR) negative after recent COVID-19 infection and histopathological report suggestive of Acute Invasive Fungal Rhinosinusitis- Mucormycosis of all ages and sex were included in the study.

### Exclusion criteria

Patients who were tested RT PCR positive and negative histopathological report for mucormycosis were excluded from the study.

### Investigations

Computed tomography scans for chest, nose, paranasal sinuses and Magnetic resonance imaging for orbit, brain was obtained for all the patients included in the study.

Nasal endoscopy was done and the samples were taken for Potassium hydroxide (KOH) mount and fungal culture. Patients were biopsied for histopathological confirmation of mucormycosis.

### Interventions

Surgical procedure was planned according to the patient's findings. Endoscopic, open and combined approaches were utilized with debridement to clear the disease. Post

**Table 1** Symptoms and signs with their percentage of presentation

Symptoms/Signs	Percentage
Facial swelling	18.2%
Nasal discharge	1%
Facial pain	18.4%
Headache	20.3%
Ophthalmoplegia	2.9%
Proptosis	9.7%
Eye swelling (Periorbital edema)	20.5%
Ptosis	2.9%
Chemosis	3.9%
Decreased vision	8.7%
Gingival swelling	18.5%
Palatal necrosis/ulcer	12.7%
Cranial nerve (CN) palsy	1.9% (CN VII)
Altered mental status	4.6%

operatively antifungal medications consisted of Amphotericin (intravenous) followed by Posaconazole (peroral).

## Results

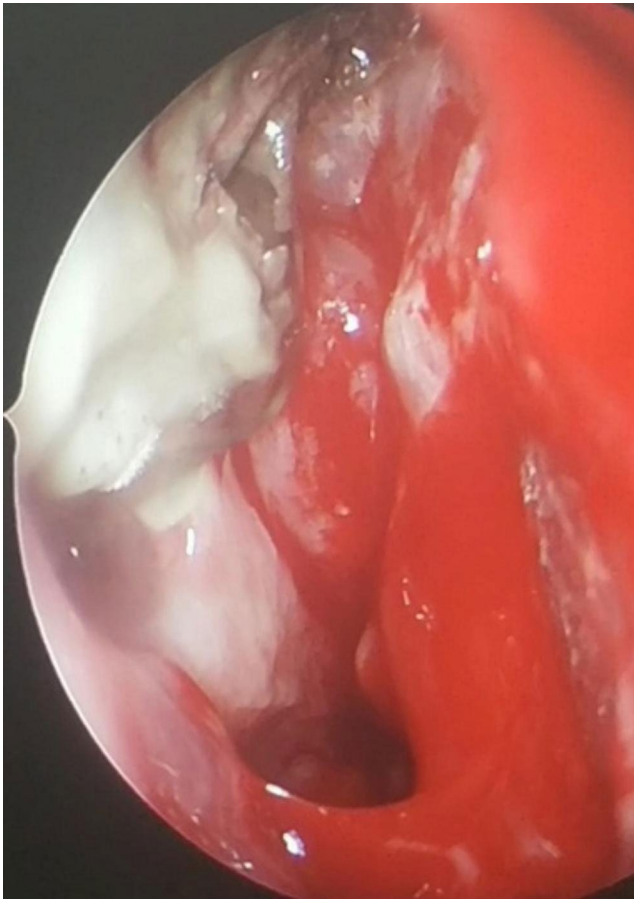
110 patients were diagnosed with Post COVID-19 Mucormycosis. The mean age was 48.42 (range 26–85). The sex distribution was 71.0% males and 29.0% females. The most common associated risk factor was diabetes mellitus 88.2% with de-novo 24.5% and known diabetes 63.7%.

The sino-nasal, orbital, palatal and intracranial involvement were 57.9%, 48.6%, 12.7% and 5.6% respectively. The summary of presenting symptoms and signs is presented in Table 1:

Palatal involvement included 5.8% for right side and 6.8% for left side with one patient having extension of ulcer to the midline. Skin was involved in one of the patients where there was necrosis of cheek area extending lower eyelid on right side.

During COVID-19 infection, 54.4% required hospitalization. Among the hospitalized, 51.5% required oxygen support and 16.5% took injection Remdesivir (six doses). A total of 66 patients were given corticosteroid therapy during COVID-19 treatment. Among the home quarantine 23% took oral steroids for COVID-19 infection.

All the patients underwent Endoscopic Sinus Surgery (ESS) and debridement of the both the sides. The most common findings included pale or necrotic mucosa, nasal crusting, thick mucopurulent discharge more on the right side (Figs. 1 and 2). Endoscopic debridement included uncinectomy, wide middle meatal antrostomy, resection of inferior and middle turbinate, anterior and posterior ethmoidectomy, sphenoidotomy, frontal sinusotomy with Table 2 showing most commonly involved site along with their percentage.



**Fig. 1** Showing necrotic unciniate process with fungal spores and fungal debris in maxillary sinus

Orbital involvement was managed by orbital decompression, intra-orbital / retro-orbital amphotericin injections, orbital enucleation and orbital exenteration (1.9% for right side and 1.0% for left side). Palatal involvement was managed by Maxillectomy which included either of partial or subtotal (8.8% with right 2.9%, left 4.9% and 1% bilateral) followed by temporary obturator insertion.

Mycological analysis by potassium hydroxide (KOH) mount revealed 50.7% as no fungal elements and fungal culture revealed *Mucor species* in 40.3%. Histopathological examination showed numerous broad ribbon-like, aseptate hyphae with right angle branching surrounded by acute inflammatory cells and presence of angioinvasion suggestive of *Mucormycosis* (Fig. 3). Special fungal stains such as Gomori Methenamine Silver (GMS) stain was also used to confirm the diagnosis.

Liposomal Amphotericin injections were given to all the patients who underwent debridement. The dosage depended on the intraoperative findings (3–5 mg/kg\* body weight, intravenous, once daily) and the duration ranged from 3 to 14 days. In patients with suspected intracranial extension, the dose of Liposomal Amphotericin injections ranged from

5 to 10 mg/kg body weight for a duration up to three weeks. At the time of discharge, the patients were prescribed tablet Posaconazole 300 mg (twice daily on day 1 and once daily from day 2 onwards until clinically negative).

The overall survival rate was 95.32% and mortality rate was 4.68%. Early cases showed better results with surgical debridement and Amphotericin injections unlike the late cases with intracranial extension.

On applying P test, there was no statistically significant association between usage of steroids, diabetes mellitus status and presentation of symptoms with duration of hospitalisation.

\*mg/kg = milligram/kilogram.

## DISCUSSION:

Fungal infections were observed in severe acute respiratory syndrome (SARS) patients and were considered the leading cause of death in 25–73.7% of patients [4][5][6]. The notably rise in number of mucormycosis has gained attention in post COVID-19 due to its immunocompromised state. The incidence of invasive fungal sinusitis is still unknown [7]. deShazo et al. described three forms of invasive fungal rhinosinusitis: granulomatous, chronic, and acute fulminant. Acute Invasive Fungal Rhinosinusitis (AIFRS) is an opportunistic infection that affects severely the immunocompromised individuals. The AIFRS is used to describe fungal sinusitis when vascular invasion is histopathologically prominent and the disease duration is less than 4 weeks [8]. The most common fungal agents that cause AIFRS are Mucoraceae and Aspergillus though Mucoraceae are less frequent [9–12]. Patients with poorly controlled diabetes mellitus are susceptible to mucormycosis [9]. An acidic environment and high glucose concentration, such as in diabetic ketoacidosis, are ideal conditions for Mucoraceae [13, 14]. In other pre COVID studies, the most common concomitant disease was diabetes mellitus [15–22]. This is in accordance with my present study as the most common associated risk factor was diabetes mellitus (88.2%) [7].

The most common presenting complaints in the present study were eye swelling (periorbital edema 20.5%), headache (20.3%), gingival swelling (18.5%), facial pain (18.4%) and facial swelling (18.2%). According to Noha et al. [7] the presenting complaints were headache and facial pain (75%), facial numbness (66.7%), ophthalmoplegia and visual loss (63.9%). Previous publications discussing the non-COVID AIFRS by Abu El-Naaj reported resembling sinusitis, facial swelling, fever [23], Kursun et al. [15] listed fever (79%), periorbital cellulitis (75%) and periorbital edema (70%) while Ketenci et al. reported fever, facial edema, facial pain and nasal obstruction [18].



**Fig. 2** Showing necrosed inferior turbinate

**Table 2** Intraoperative findings with their percentage of involvement

Sites	Percentage
Inferior turbinate	15.7%
Middle turbinate	21.8%
Uncinate process	10.8%
Septum	19.6%
Maxillary sinus	78.4%
Anterior Ethmoids	35.3%
Posterior Ethmoid	35.3%
Sphenoid	16.7%
Frontal sinus	4.9%
Skull base	2.9%
Pterygopalatine fossa	5.9%
Sphenopalatine artery	3.9%

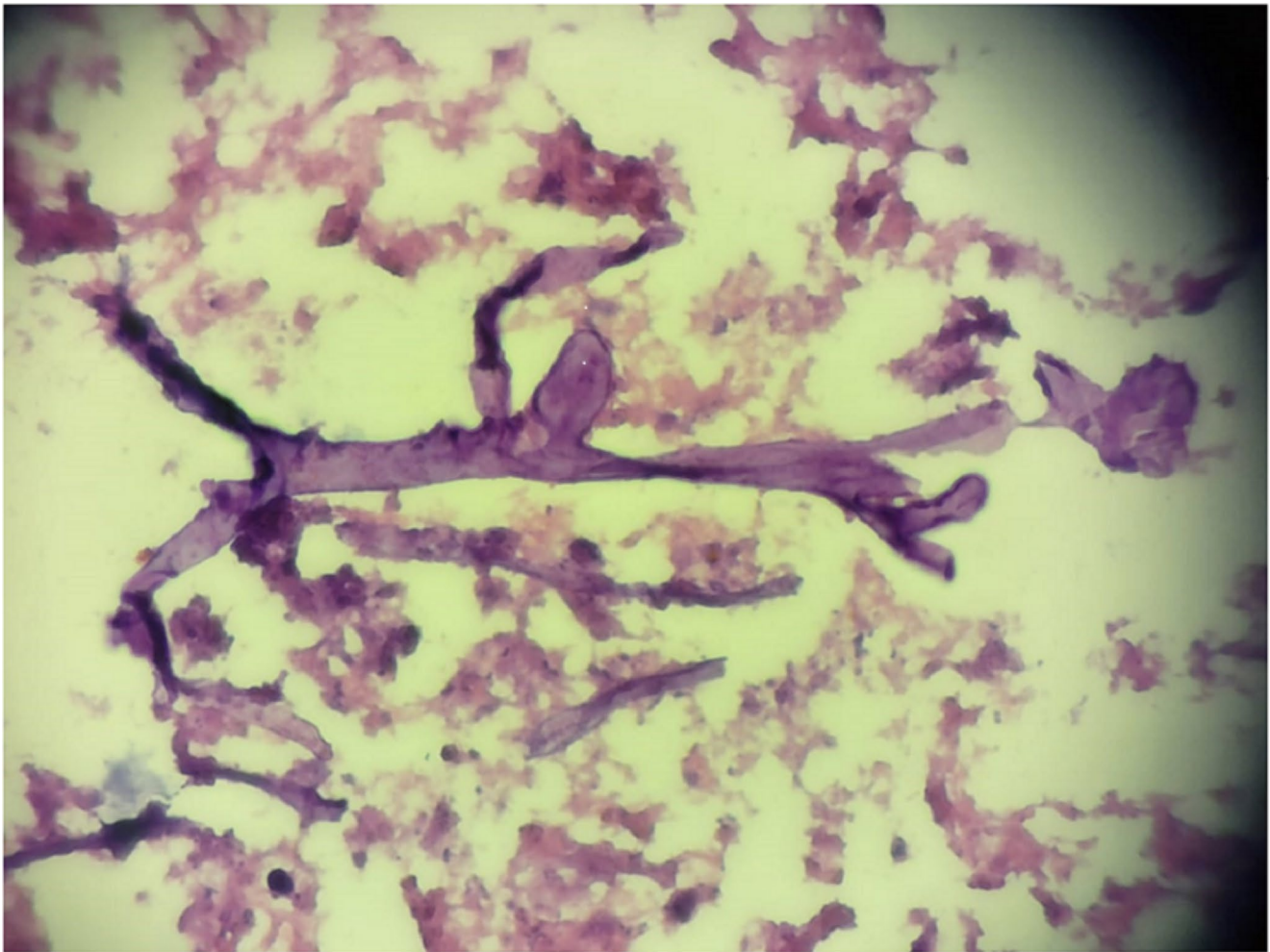
Disease limited to nasal cavity occurs during the early stages therefore nasal examination with endoscope should be done in patients with clinical suspicion. White discoloration of the mucosa is indicative of ischemia while black discoloration is indicative of necrosis [9][24]. Non-COVID AIFRS publications by Gillespie et al. [24] reported that mucosal abnormalities were most commonly seen on the middle turbinate (67%), followed by the septum (24%), hard palate (19%), and inferior turbinate (10%) while study by

Ahmet et al. [9] the lesions were most commonly observed in the septum (12 patients, 63.2%), the middle turbinate in 11 (57.9%) patients, of the inferior turbinate (8 patients, 42.1%) and hard palate (3 patients, 15.8%). In contrast to the previous studies, our study showed involvement of the maxillary sinus (78.4%), anterior ethmoids (35.3%), posterior ethmoids (35.3%) and middle turbinate (21.6%) more on right side.

The mainstay of treatment includes antifungal agents and aggressive surgical debridement [10, 25, 26]. In the present study all the patients were surgically treated by endoscopic debridement but were 88.23% were exclusive debridement unlike the study conducted by Noha et al. [7] where 66.7% of cases underwent exclusive endoscopic debridement and in non-COVID AIFRS study by Turner et al. [3] performed endoscopic approach in 46.4% of their patients. Orbital exenteration were performed in 2.9% in our study while 16.7% of cases in study by Noha et al. [7]

The majority of patients in Noha et al. [7] study received Liposomal Amphotericin B (80.56%) and eight patients with Aspergillus received Voriconazole on other the hand my study primarily focuses on mucormycosis therefore the





**Fig. 3** Showing histopathological section of mucormycosis (hematoxylin and eosin stain)

antifungal medication of choice was Liposomal Amphotericin B.

AIFRS has high morbidity and mortality rates (18–80%) despite improvements in medical and surgical management protocols [7]. The survival rates reported in studies ranges from 20 to 80% [15, 18, 24, 27]. The overall survival rate of non-COVID AIFRS cases reviewed by Turner et al. <sup>11</sup> was 49.7%, COVID AIFRS by Noha et al. [7] was 63.89% while my present study had 95.32%. The relatively better survival rate was due to early diagnosis, aggressive surgical debridement and early use of antifungal medications.

## Conclusion

Early diagnosis of AIFRS (Mucormycosis) requires a high index of suspicion because of non-specific initial symptoms and radiological signs. Biopsies of mucosal tissue from suspected sites should be performed as early as possible. Complete endoscopic debridement should be the treatment of

choice for highly suspected lesions limited to nasal cavity. More radical excision including maxillectomy and orbital exenteration may be necessary in severe cases. Aggressive surgical debridement followed by antifungal medications are the mainstay of AIFRS treatment. The extent of AIFRS and the underlying medical disease (uncontrolled diabetes) are the main factors related to the prognosis.

**Author contribution** All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Joshi Anto Tommi. J, L. Sudarshan Reddy. The first draft of the manuscript was written by Joshi Anto Tommi. J and all the authors commented on preview versions of the manuscript. All authors read and approved the final manuscript.

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**Data Availability** Not applicable.

## Declarations

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**Ethical Approval** The study protocol was approved by the Institutional Ethics Committee.

**Conflict of interest** The authors declare there is no conflict of interest.

**Consent to Participate and consent for publication** As this was a retrospective analysis of medical charts, no informed consent was taken.

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