

# Mucormycosis following COVID-19 infection-An epidemic developing in a pandemic, a case series from a tertiary care hospital of India

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## ABSTRACT

When the world is still struggling to fight the Coronavirus disease-19 pandemic, an epidemic of mucormycosis following the COVID-19 infection is increasing in India. Mucormycosis is a rare life-threatening fungal infection with a high mortality rate. Is this increase due to the rampant usage of corticosteroids, some immune dysfunction in COVID-19, uncontrolled blood sugar, increased ferritin, use of industrial oxygen, use of unsterile mask, or use of unsterile water as a humidifier in oxygen delivery systems? This remains a question. In this case series, we present five cases of rhino-orbito-cerebral mucormycosis which followed after the COVID-19 infection in these patients. We have included patients' clinical, laboratory, and radiological data in this case series and reviewed the literature.

**Keywords:** COVID-19, diabetes, mortality, mucormycosis

## Introduction

In the era of 2020s, the deadly COVID pandemic has taken millions of lives worldwide. After the emergence of the Novel Corona Virus in Wuhan, China, in December 2019, this virus has traveled throughout the globe causing suffering to humanity. Severe acute respiratory syndrome-coronavirus-2, the causative virus of this deadly pandemic continues to resurge in waves even in 2021, taking many lives. It has been observed that many COVID-19-positive patients coming to the hospital are being diagnosed with invasive fungal infections such as mucormycosis. Mucormycosis is a rare fatal fungal infection caused by a group of molds called mucormycetes. Mucormycosis mostly occurs in an immunocompromised and diabetic patient. The incidence of mucormycosis varies from 0.005 to 1.7 per

million population globally, but the Indian population on the contrary has mucormycosis prevalence as high as 0.14 per 1,000.<sup>[1]</sup> The clinical presentation of mucormycosis can be rhino-orbito-cerebral, pulmonary, cutaneous, or disseminated. The most common presentation being rhino-orbito-cerebral, followed by pulmonary, and cutaneous. The mucormycosis infection is characterized by angioinvasion and tissue necrosis. In a majority of mucormycosis cases, uncontrolled diabetes seems to be the underlying disease causing the infection. There are also case reports of mucormycosis in patients having iron and aluminum overload, patients on dialysis, and patients on iron chelator therapy.<sup>[2]</sup> For the diagnosis of mucormycosis, we need a high index of suspicion, recognition of host factors, prompt usage of imaging, histology, and microbiology. The red flag signs of mucormycosis include nasal stuffiness, epistaxis, foul-smelling nasal discharge, eye pain, eyelid edema, periocular edema, facial pain, worsening headache, proptosis, sudden loss of vision, ptosis, facial palsy, and ocular motility restriction. The rhino-orbito-cerebro mucormycosis (ROCM) can be categorized

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as possible, probable, and proven. If a patients suffering from concurrent or recently treated COVID-19, diabetes mellitus, receiving corticosteroid, tocilizumab, supplemental oxygen, develops the above red flag signs of mucormycosis then it is possible ROCM. The possible ROCM along with positive nasal endoscopy findings, or contrast-enhanced magnetic resonance imaging or computed tomography scan then it falls into probable ROCM category. Probable ROCM with microbiological confirmation is categorized as proven ROCM. The all-cause mortality of mucormycosis varies from 40 to 80% depending on the site of infection and underlying disease. The management of mucormycosis includes surgical debridement, antifungal drugs, and control of the predisposing conditions.<sup>[3]</sup>

Many factors may contribute to the increasing fungal infection following COVID-19 which include rampant use of corticosteroids, extensive lung damage caused by COVID-19, use of tocilizumab, immune dysregulation associated with COVID-19, and abnormal iron profile characteristics following COVID-19. Here we present a case series of five ROCM cases which followed after COVID-19 infection. We have included their clinical, laboratory, and radiological information.

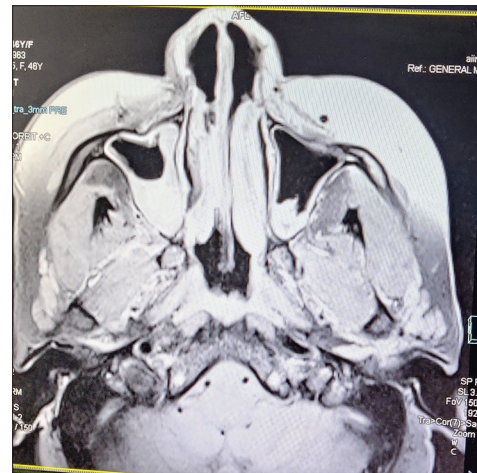
## Case History

### Case 1

A 46-year-old female had a cough and fever for 4 days. She was on regular treatment for diabetes mellitus for 7 years. Her throat swab reverse transcription–polymerase chain reaction for COVID-19 came positive. She was admitted with these symptoms in another hospital and received injection piperacillin-tazobactam, dexamethasone (4 mg three times a day), and remdesivir for 5 days. She was on oxygen support also. After 5 days of treatment, she developed right eye pain and facial swelling [Figure 1]. She presented to our hospital with these symptoms. On examination, she had tenderness over the right maxillary sinus. Laboratory investigations showed random blood sugar (RBS) 307 mg/dL, glycated hemoglobin 9.8%, hemoglobin 8.3 gm/dl, white blood cell count 8320/cumm, C-reactive protein 78 mg/L, and serum ferritin 38 ng/mL. MRI of the brain with paranasal sinuses (PNS) showed pansinusitis with multiple non-enhancing mucosal components in the bilateral maxillary sinuses, right posterior ethmoidal air, and right inferior turbinate suggestive of an invasive fungal infection [Figure 2] From this MRI report, a diagnosis of probable ROCM was made and she was prescribed liposomal amphotericin B (LAMB). Functional endoscopic sinus surgery (FESS) was performed and the necrotic material was sent for potassium hydroxide (KOH) mount and histopathology. The histopathology report showed the presence of fungal hyphae, aseptate to pauci septate with the presence of angioinvasion, fibrin thrombi, and septic emboli suggestive of rhinosinusitis with mucormycosis with angioinvasion. The KOH mount revealed broad pauci septate hyphae suggestive of mucormycosis [Figure 3] Clinically, she improved with treatment and was advised to continue liposomal amphotericin B for 3 weeks.



**Figure 1:** Right-sided facial swelling



**Figure 2:** MRI of the brain post-contrast axial section showing the right maxillary sinusitis



**Figure 3:** KOH mount showing broad septate ribbon-like fungal elements

### Case 2

A 55-year-old male, a case of diabetes mellitus for 10 years, had a history of fever and breathlessness for 8 days. His throat swab



RT-PCR for COVID-19 came positive. The patient was admitted to another hospital and received injection dexamethasone 12 mg/day for 4 days followed by tablet methylprednisolone 16 mg/day for 3 days. The patient was referred to our hospital with complaints of increasing breathlessness, left eye pain, and difficulty in opening the left eye [Figure 4]. The patient was maintaining 95% oxygen saturation on 10 L/min oxygen support. On examination of the oral cavity, there was oral thrush. A suspicion of ROCM with oral candidiasis was kept. The laboratory investigation showed random blood sugar 562 mg/dL, HbA1c 10.2%, hemoglobin 15.3 g/dL, WBC count 4840/cumm, CRP 129 mg/L, and serum ferritin 155.82 ng/mL. The KOH mount of oral scraping showed budding yeast with pseudohyphae s/o candidiasis and that of nasal smear showed broad pauci septate hyphae s/o mucormycosis. Contrast enhanced computed tomography of the brain with PNS showed soft-tissue opacification in bilateral ethmoid, frontal, sphenoid sinuses, and maxillary sinuses with obliteration of bilateral osteomeatal complex. Subtle central hyperdense contents in the sphenoid sinus with surrounding hypodense mucosal thickening were also seen (s/o fungal sinusitis). The patient was started on LAMB, but the next day, the patient succumbed due to respiratory failure.

### Case 3

A 75-year-old male, a known case of diabetes mellitus since 2006, alcoholic liver disease, hypothyroid since 2000, was admitted in another hospital for 5 days with severe COVID-19 and was referred to our hospital with a right eye swelling along with pain. Prior treatment records outside of the hospital were not available with the patient. He was drowsy at the time of admission. The oral cavity examination revealed black discoloration of the hard palate. The ocular examination revealed right eye ptosis, mild proptosis, chemosis, and redness of the conjunctiva. The ocular movements were absent on the right side. Injection LAMB was started based on suspicion of mucormycosis. The laboratory investigation revealed RBS 270 mg/dL, HbA1C 8.2%, hemoglobin 10.3 g/dL, WBC count 5000/cumm, CRP 86 mg/L, and serum ferritin 112 ng/mL. MRI of the brain with PNS showed mucosal thickening in all sinuses with air-fluid level in the right half of the sphenoid sinus. There was also extensive soft-tissue edema in the right eye region [Figure 5]. On MR, the angiogram of the right internal carotid artery is not visualized throughout its entire extent, these overall features are suggestive of invasive fungal sinusitis probably ROCM [Figure 6]. The KOH mount of the nasal smear showed no fungal elements. Despite all efforts, the patient expired after 2 days of admission.

### Case 4

A 42-year-old male with no comorbidities was hospitalized with severe COVID-19 and received injection amoxiclav, injection dexamethasone (8 mg twice a day for 5 days) along with other supportive treatment. He was referred to our hospital due to increasing breathlessness, loss of vision, and pain in the right eye. The right eye examination showed visual acuity perception



Figure 4: Left eye ptosis

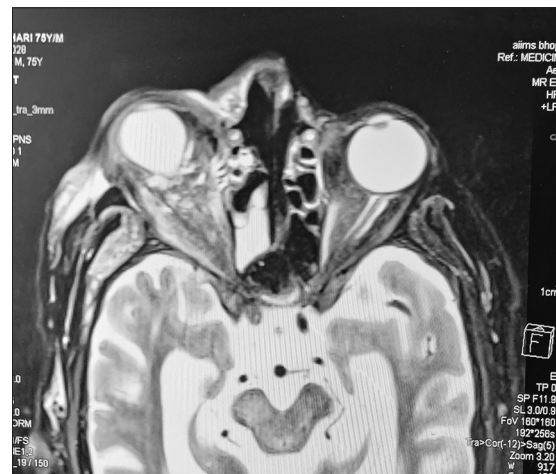


Figure 5: MRI of the brain axial section showing right-sided orbital cellulitis

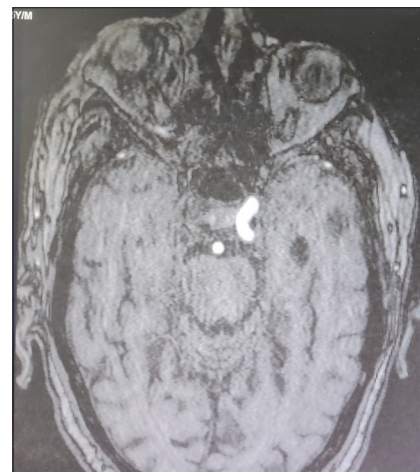


Figure 6: MRI of brain angiography showing the right internal carotid artery thrombosis

of light only, restricted ocular movement, periorbital swelling, and congestion. The left eye had visual acuity of 6/36. The laboratory investigation revealed RBS 380 mg/dL, HbA1C 6.2%, hemoglobin 11.3 g/dL, WBC count 4840/cumm, CRP

56 mg/L, and serum ferritin 74 ng/mL. The KOH mount of the nasal smear showed no fungal elements. His MRI of the brain with PNS revealed pansinusitis, right orbital cellulitis with optic neuritis—findings suggestive of invasive fungal infection probably mucormycosis. The patient was started on LAMB and underwent functional endoscopic sinus surgery. Irrespective of all efforts in managing this patient, the patient succumbed to death after 10 days of admission.

### Case 5

A 40-year-old male with no comorbidities was admitted with severe COVID-19 in a hospital and received injection amoxiclav, injection dexamethasone (8 mg twice a day for 7 days) along with other supportive treatment. He was referred to our hospital for left eye pain and diminution of vision from the left eye. The laboratory investigation revealed RBS 140 mg/dL, HbA1C 6%, hemoglobin 12.4 g/dL, WBC count 9000/cumm, CRP 87 mg/L, and serum ferritin 78 ng/mL. The MRI scan showed left orbital cellulitis with pansinusitis. On admission, the patient was maintaining a saturation of 97% on room air. The patient was started on LAMB. The corticosteroid was stopped. Left nasal endoscopic debridement with orbital decompression was done the next day. The histopathology report showed foci of necrosis with thin, broad, eosinophilic ribbon-shaped fungal hyphae with foci of angioinvasion and fibrin thrombi. The KOH mount showed abundant broad aseptate hyphae suggestive of mucormycosis. The fungal culture showed *Rhizopus arrhizus*. The patient was discharged in stable condition after 28 days of LAMB.

## Discussion

Mucormycosis is a rare disease, which can cause diagnostic and therapeutic challenges for centers that are not familiar with it. This causes delays in recognition and treatment. The global guidelines for mucormycosis published by the European confederation of medical mycology strongly supported the early complete surgical treatment of mucormycosis whenever possible. They also suggested the usage of liposomal amphotericin as the first-line antifungal treatment at the dose ranging from 5 mg/kg to 10 mg/kg. Isavuconazole and posaconazole are the other drugs available for its treatment. The European confederation guidelines support treatment until permanent reversal of immunosuppression and complete response on imaging.<sup>[4]</sup>

Recently, the systemic review of mucormycosis cases in COVID-19 published on May 2021 included 101 cases of mucormycosis of which 82 are from India. In this review, diabetes was present in 80% of the cases and a corticosteroid was given in 76.3% of cases.<sup>[5]</sup> Sarkar *et al.*<sup>[6]</sup> studied 10 cases of mucormycosis in COVID-19 and found that all patients were diabetic, 9 patients required ventilatory support, and all of them had a history of intake of corticosteroid. A study by Ravani *et al.*<sup>[7]</sup> from India included 31 patients with rhino-orbital mucormycosis during the COVID-19 pandemic and found that the mean age of the patients

was 56.3 years; 96.7% of the patients had uncontrolled diabetes, and 61.2% of the patients received corticosteroids. A study by Mritika Sen *et al.*<sup>[8]</sup> included six patients with COVID-19 who developed ROCM and found that the mean duration between the diagnosis of COVID-19 and development of symptoms of mucormycosis was  $15.6 \pm 9.6$  days. All of the above patients underwent surgery and all were alive on the follow-up visits. Bhattacharyya A, *et al.*<sup>[9]</sup> searched comprehensive literature using keywords mucormycosis, rhino-orbital-cerebral-mucormycosis, COVID-19, and SARS-CoV-2 (from November 01, 2019, to June 30, 2021). Their study showed that indiscriminate use of corticosteroids has led to the mucormycosis epidemic, especially in patients with preexisting diabetes mellitus with higher mortality.

In our case series of five cases, three cases are categorized as proven ROCM and two cases are categorized as probable ROCM. All patients had a history of corticosteroid intake previously. Corticosteroid drugs were stopped in all the cases after a diagnosis of mucormycosis was made. Three out of five cases were diabetic though blood sugar was raised at the time of admission in all the cases most probably due to steroid-induced hyperglycemia. Out of the five patients, three patients succumbed to death within 1 month of admission. The two patients who survived had undergone surgical debridement. All the above patients were on supplemental oxygen at least once during their hospitalization. There is a need for primary care physicians to be more aware of the likelihood of mucormycosis in COVID-19 patients, as a delay in diagnosis can result in severe morbidity and mortality.

## Conclusion

If any COVID-19 patient develops red flag signs of mucormycosis, the primary care physicians should always have a suspicion of mucormycosis and these patients should be referred to the tertiary care center. Early surgery and early initiation of the antifungal drug are associated with a better outcome. The corticosteroids in COVID-19 should be used cautiously to avoid the unwanted consequences following it.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

## Key message

Mucormycosis is a rare fatal fungal infection caused by a group of molds called mucormycetes. Mucormycosis mostly occurs in an immunocompromised and diabetic patient. For the diagnosis of mucormycosis, we need a high index of suspicion,

recognition of host factors, prompt usage of imaging, histology, and microbiology. Red flag signs of mucormycosis include nasal stuffiness, epistaxis, foul-smelling nasal discharge, eye pain, eyelid edema, facial pain, worsening headache, proptosis, sudden loss of vision, ptosis, and facial palsy. If any COVID-19 patient develops red flag signs of mucormycosis, primary care physicians should always have a suspicion of mucormycosis and these patients should be referred to the tertiary care center. Early surgery and early initiation of antifungal drugs are associated with a better outcome.

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### Conflicts of interest

There are no conflicts of interest.

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