

## SINONASAL MUCORMYCOSIS. A RETROSPECTIVE ANALYSIS OF CLINICAL FEATURES AND TREATMENT OUTCOMES

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Received : 03/01/2024  
Received in revised form : 25/02/2024  
Accepted : 12/03/2024

**Keywords:**

Mucormycosis, incidence, Diabetes mellitus, Amphotericin B.

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DOI: 10.47009/jamp.2024.6.2.62

Source of Support: Nil,  
Conflict of Interest: None declared

*Int J Acad Med Pharm*  
2024; 6 (2); 296-299



### Abstract

**Background:** In patients with limited Sino-nasal disease in this Covid pandemic we suspect invasive Fungal sinusitis especially mucormycosis. We are presenting our series of patients who presented to our center with symptoms of suspected Mucormycosis for which we have done combined modality of treatment which includes control of metabolic abnormality, administration with early starting of Anti-Fungal medication - Amphotericin B and surgery-sino-nasal debridement that spans simple sinus clearance. Recent literature includes anecdotal descriptions of successful treatment with combined modality of management. We evaluated the clinical features and outcome of treatment for the different stages of limited Sino-nasal mucormycosis. **Material and Methods:** Outcome for each group was measured as "Treatment success" (disease free, stable patient with metabolic abnormality under control) and "Treatment failure" (progression of disease with worsening general condition or mortality due to the disease). **Results:** A total of 25 patients diagnosed sino nasal mucor mycosis were included for the analysis. Majority of patients had underlying diabetes mellitus (n=19), of which five patients were recently diagnosed during their COVID-19 illness. Eight patients had concomitant diabetic ketoacidosis. In our study 16 patients out of 25 were on oxygen therapy. Sino-nasal symptoms like nasal stuffiness, nasal discharge and epistaxis were present in 40%, 23% and 16% of patients respectively. Rhino-orbital was the most common variety. The categorization of the patients as per the proposed staging system for ROCM. Our study showed that 12 patients was in Stage 1 and rest had disease severity stage 3b or less. In our study, 92% had treatment success, as they were alive and well with regression of ROCM and rest 8% (n=2) had expired as a part of treatment failure. **Conclusion:** Debridement of the sinuses is necessary in all cases of rhino-sinal mucormycosis. Diagnosis in the early stage needs a high degree of suspicion. There is a definite role for early starting of Amphotericin B, retention of orbits in patients whose metabolic derangement is rapidly controlled and orbital involvement is non-progressive. The rise in the number of cases, the emergence of new risk factors and causative agents, and the challenges in managing the disease are important concerns with mucormycosis in India.

## INTRODUCTION

Mucormycosis is an angioinvasive disease that is characterized by tissue infarction and necrosis. The novel severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) first reported in Wuhan, China on 21 December 2019.<sup>[1,2]</sup> As of June 2021, 172 million people have been affected by this virus with 3.69 million deaths worldwide.<sup>[3]</sup> The most common presenting complaints of this disease include cough, fever, and dyspnea.<sup>[4]</sup> The clinical presentations of mucormycosis are classified on the

basis of anatomic localization, such as rhino-orbital-cerebral (ROCM), pulmonary, gastrointestinal, cutaneous, renal, and disseminated mucormycosis. Patients with diabetes mellitus, haematological malignancy and chemotherapy, hematopoietic stem cells, and solid-organ transplant recipients on immunosuppressive therapy, with iron overload, on peritoneal dialysis, extensive skin injury, human immunodeficiency virus (HIV) infection and voriconazole therapy are at increased risk of acquiring mucormycosis. A considerable number of mucormycosis cases are reported in

immunocompetent hosts. Though mucormycosis is globally distributed, certain risk factors, clinical forms, and causative agents of the disease are prevalent in India. Uncontrolled diabetes mellitus is the most common underlying disease associated with mucormycosis in India, in contrast to hematological-malignancy patients and solid organ transplant recipients in developed countries.<sup>[5,6]</sup>

The pathogens associated with mucormycosis varies considerably between India and developed countries. Globally, *Rhizopus arrhizus* is the commonest cause of mucormycosis. The *Apophysomyces* species ranks second in India compared to the *Lichtheimia* species in developed countries. Infections due to *Rhizopus microsporus* and *Rhizopus homothallicus* are rising in India. The rise in incidence over the years at that centre may be due to improved awareness and expertise in diagnosing the disease, though the possibility of a real rise in incidence cannot be ruled out.<sup>[7,8]</sup>

Diabetes mellitus is a common predisposing factor for the ROCM type of disease. In recent Covid Pandemic patients with pulmonary symptoms have been started on corticosteroid, these patients develop symptoms of invasive fungal sinusitis in Post-Covid period due to uncontrolled Diabetes mellitus and also due to microvascular thrombophlebitis.

A recent multi center study from India reported that 77% of ROCM cases were in the diabetic population. Different case series focused on ROCM cases from India reported diabetes as a risk factor in 80–100% of cases. Trauma is a risk factor for the ROCM type (15–52%), mainly after unhygienic dental procedures during tooth extraction

Pulmonary mucormycosis is commonly associated with SOT recipients (37–44%), haematological malignancy (10–26%), and diabetes mellitus (10–14%) in Indian patients. These findings were similar to those of global data, haematological malignancy (34–44%) is the most common risk factor associated with pulmonary mucormycosis, followed by diabetes mellitus (13–14%). A review on pulmonary mucormycosis reported haematological malignancy (40%), diabetes mellitus (36%), CKD (17%), and SOT (6%) as significant underlying diseases.

In India, post pulmonary tuberculosis (38%) is a new risk factor for pulmonary mucormycosis. The cutaneous type is seen in 10–31% of patients with mucormycosis after trauma following road traffic accidents, burn wounds, intramuscular injection, intravenous catheters, adhesive tapes, and surgical-site infections.

The treatment of mucormycosis involves the early initiation of therapy, the surgical debridement of infected tissue, antifungal therapy, and managing the underlying disease. Amphotericin B (Amp B) is the first-line drug of choice; subsequently, posaconazole and isavuconazole are prescribed. The major drawbacks in managing mucormycosis in India are a gap in treatment protocol and the financial constraints of patients that they cannot afford liposomal Amphotericin B. Posaconazole and

isavuconazole were used as salvage therapy in the treatment of mucormycosis.

The mortality rate of mucormycosis in India is in the range of 28%–52%. The mortality rate in different clinical forms of mucormycosis reported from India are ROCM (31%–49%), pulmonary (61%–77%), cutaneous (23%–57%), gastrointestinal (67%–94%), and disseminated (62%–79%). In the present study, we discuss the epidemiology, risk factors and underlying diseases, causative agents, and clinical outcomes associated with mucormycosis in the Indian population.

## MATERIALS AND METHODS

This was a retrospective, single-center, observational study. The study was conducted in the Department of ENT at a tertiary care teaching hospital. Study cases were included between March 2021 and November 2022. We observed a surge in mucor mycosis cases in May and June with 25 cases of mucormycosis underwent surgery during the study period. We planned to conduct this study to delineate the clinico- epidemiological profile of ROCM. ROCM was defined as patients with MM along with acute or recent COVID-19 illness. The ethical approval was obtained from the Institute Ethics Committee before the commencement of the study.

Information was collected, from the hospital records with an emphasis on the demographic profile, date of arrival, date of onset of symptoms, clinical features of ROCM, clinical features, detailed comorbidities and risk factors, steroid usage details for COVID-19, radiological and microbiological evaluation. Outcome for each group was measured as "Treatment success" (disease free, stable patient with metabolic abnormality under control) and "Treatment failure" (progression of disease with worsening general condition or mortality due to the disease). All the analyses were performed with IBM SPSS. Version 24.0.

## RESULTS

A total of 25 patients diagnosed sino nasal mucor mycosis were included for the analysis. The median age of the included patients was 46.9 years, with a range of 26-72 years, with 88% males. Majority of patients had underlying diabetes mellitus (n=19), of which five patients were recently diagnosed during their COVID-19 illness. Eight patients had concomitant diabetic ketoacidosis.

An important risk factor for ROCM was the use of steroids for COVID- 19. A total of 18 patients (72%) had received steroids for COVID-19 disease prior to arrival. Systemic steroids were prescribed for a median duration of 7.5 days in these patients.

In our study 16 patients out of 25 were on oxygen therapy. Most common symptom reported in ROCM was related to the eye and its adnexal tissues. Sino-

nasal symptoms like nasal stuffiness, nasal discharge and epistaxis were present in 40%, 23% and 16% of patients, respectively. Nearly 82% patients had eye pain, swollen eyes and significant lid edema on examination. Other ophthalmic symptoms were diminution of vision, proptosis, ptosis and double vision. On examination of nasal cavity, crusting and ulceration were present in 25% patients. Another common symptom was headache, which was the presenting complaint in most of the cases

For definitive diagnosis of ROCM, microbiological samples were taken from the active lesions (with or without nasal endoscopy). Potassium hydroxide (KOH) mount with calcofluor stain was positive for aseptate hyphae in many patients (63%). Radiological diagnostic modalities included contrast-enhanced computed tomography of brain, orbit and paranasal sinuses. Most common radiological diagnosis was rhinosinusitis, followed by orbital extension and intracranial invasion. After clinical, microbiological and radiological workups, final diagnosis was made Rhino-orbital was the most common variety.

Along with the stabilization of hemodynamic parameters, all the ROCM cases were managed with initiation of systemic antifungals as soon as possible. Intravenous liposomal amphotericin—B or oral posaconazole was initiated. Control of underlying comorbid illness including insulin therapy for hyperglycemia was initiated for all. Urgent ophthalmology and neurosurgery consultations were taken for shared decision on the surgical debridement pathway.

CT scan was done for all patients and MRI for those who needed. Diffuse PNS involvement was seen in 56% and bilateral PNS involvement was seen in 38%. In the orbit, diffuse involvement predominated in 29% followed by involvement of the medial orbit in 18%. In the CNS, cavernous sinus was most commonly involved in 10%. The categorization of the patients as per the proposed staging system for ROCM. Our study showed that 12 patients was in Stage 1 and rest had disease severity stage 3b or less.

Primary initiation of medical management with amphotericin B was preferred in most of cases. Primary functional endoscopic sinus surgery (FESS)/PNS debridement was performed in almost all cases in our study as one of important inclusion criteria is patient who underwent surgery. Of 25 patients for in our study, 92% had treatment success, as they were alive and well with regression of ROCM and rest 8% (n-2) had expired as a part of treatment failure.

## DISCUSSION

We conducted a single-center, retrospective study of 25 patients with mucor. As the number of covid associate mucormycosis cases were increasing in

India during the second wave of COVID-19 pandemic, we have tried to delineate the clinico-epidemiological profile of these patients.

Majority of the patients in our study were middle-aged, of which nearly two-thirds were male. This demographic profile was similar to the population of 82 patients studied by Sharma et al,<sup>[9]</sup> of which two-third were male and aged between the ages 31–60 years. Many experts believe that the combination of high dose steroids and uncontrolled diabetes has led to this epidemic of MM in COVID-19 patients. In the setting of COVID-19, case series by Sharma et al<sup>9</sup> described diabetes as a risk factor in 90% cases of which 52% had uncontrolled disease. Our study has reflected their findings.

Prolonged use of corticosteroids increasing risk of MM has been reported in patients. Ribes et al,<sup>[10]</sup> described that acute or chronic use of steroids in such patients predisposed them to fungal infection. Steroid use during the pandemic has been supported by the Randomized Evaluation of COVID-19 Therapy trial, only in those receiving supplemental oxygen therapy and has been endorsed by major international guidelines.

Patterns of MM in patients can differ based on their risk factors, e.g. sinus involvement is common among diabetics. Presence of associated facial erythema, perinasal swelling, nasal ulcers or eschar should serve as early pointers. The red flag signs to look for are cranial nerve palsy, diplopia, periorbital swelling, proptosis, orbital apex syndrome, sinus pain and palatine ulcer.

In the background of COVID-19, Satish et al,<sup>[11]</sup> reported that 48% of patients in their case series had rhino-orbital disease followed by rhino-orbito-cerebral form. Our study too had most common features related to rhino-orbital followed by rhino-orbito-cerebral type. Microbiological diagnosis was confirmed by KOH-calcofluor mount showing aseptate hyphae and extent was assessed with contrast- enhanced computed tomography scans as per guidelines. All patients in our study were started on systemic antifungals and majority received liposomal amphotrecin B

Diagnostic nasal endoscopy allows a quick inspection and sampling from the nasal cavity. It is a simple, bedside yet powerful tool to diagnose suspected cases in stage 1 and early stage 2 before the clinical and radiological signs are evident. Rapid diagnosis of mucormycosis can be achieved with direct microscopy using KOH wet mounts, with or without fluorescent brighteners like blankophor and calcofluor white, and this was done in 85% of the cases that we analysed. In ROCM, where early diagnosis is the key to survival, these resources should be harnessed and made more widely available.

The management of mucormycosis essentially involves control of hyperglycaemia or any other risk factor, optimal surgical debridement, and medical management with antifungal agents. Amphotericin B is the antifungal drug of choice for mucormycosis.

In a previous study it has been used in 78% of the patients of COVID-19-associated ROCM.<sup>[9]</sup> The liposomal form is preferred since it is less nephrotoxic and, therefore, higher doses may be given for a prolonged duration. A study from India has shown posaconazole to be highly effective as salvage therapy for ROCM with life salvage and complete resolution in 67% of the patients.<sup>13</sup>In our study, 20 % of the patients received combination therapy with posaconazole being the preferred drug added to amphotericin B.

ROCM is a rapidly progressive disease, with 30–90% mortality rate in cases with cerebral involvement.<sup>[12,14]</sup> For cases associated with COVID-19, the overall mortality has been estimated to be 31%.<sup>15</sup> Results from our study show that overall, the mortality with COVID-19-associated ROCM is 8%. These results are likely to change over time as the patients are followed up. Based on our results, it is clear that the proposed staging corresponds to the severity of the disease as well as the survival outcome.

## CONCLUSION

The exact prevalence of mucormycosis in India is unknown, though the estimated prevalence is much higher than that in developed countries. The possible reason for the high prevalence is the abundant presence of Mucorales in the community and hospital environment, large number of susceptible hosts especially diabetics, and the neglect for regular health check-ups of Indian population. A considerable number of patients are ignorant of diabetes status till they acquire mucormycosis. Though uncontrolled diabetes is a common risk factor in all types of mucormycosis, it is significantly associated with ROCM type. Other emerging risk factors of mucormycosis are pulmonary tuberculosis, chronic kidney disease, and critically ill patients. In this post Covid situation being irrational use of Corticosteroids during Covid infection.

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