



## MANAGEMENT, AND OUTCOME OF COVID-19-ASSOCIATED RHINO-ORBITAL-CEREBRAL MUCORMYCOSIS IN GDMCH

Dr S.senthil  
Kumaran\*

MS (ENT), Associate Professor Government Dharmapuri Medical College and Hospital Dharmapuri\*Corresponding Author

**ABSTRACT** **Introduction:** COVID-19-associated rhino-orbital-cerebral mucormycosis (ROCM) has reached epidemic proportion during India's second wave of COVID-19 pandemic, with several risk factors being implicated in its pathogenesis. This study aimed to determine the patient demographics, risk factors including comorbidities, and medications used to treat COVID-19, presenting symptoms and signs, and the outcome of management. **Methods:** This was a retrospective, single-centre, observational study. The study was conducted in the Department of ENT at a tertiary care teaching institute of India. Between March 2021 and November 2021, our hospital treated 6418 COVID-19 confirmed patients. We observed a surge in mucor mycosis cases in May and June with 100 cases reported upto November. **Results:** Of the 100 patients in our study the mean age of patients was 52.8 years with a male preponderance, While 57% of the patients needed oxygen support for COVID-19 infection, 79% of the patients were treated with corticosteroids. Overall treatment included intravenous amphotericin B, functional endoscopic sinus surgery (FESS)/paranasal sinus (PNS) debridement, orbital exenteration. At final follow-up, mortality was 6%. **Conclusion:** Corticosteroids and DM are the most important predisposing factors in the development of COVID-19-associated ROCM. COVID-19 patients must be followed up beyond recovery. Awareness of red flag symptoms and signs, high index of clinical suspicion, prompt diagnosis, and early initiation of treatment with amphotericin B, aggressive surgical debridement of the PNS, and orbital exenteration, where indicated, are essential for successful outcome.

**KEYWORDS :** ROCM, mucormycosis, COVID 19, management.

### INTRODUCTION

Mucormycosis in humans caused by the mucorales group of fungi. Inhalation of fungal spores is harmless in immunocompetent individuals but can cause life-threatening disease in those who are immunocompromised. 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>. Extra pulmonary manifestations comprise alteration of taste, olfactory changes, erythematous rashes and urticaria, and even severe neurologic complications like altered consciousness, dizziness, and cerebrovascular events<sup>5</sup>. Due to the severe inflammatory reaction and diffuse alveolar damage, COVID-19 patients experience a decline in their CD-4+ and CD-8+ T cell count, making them susceptible to a wide range of infections, particularly fungal infections<sup>6</sup>. The inevitable duo of COVID-associated mucormycosis (CAM) releases a pro-inflammatory cytokine storm of IL-6 and IFN- $\gamma$  in the infected individual. The coronavirus infection increases vascular damage to endothelial cells and promotes endotheliitis. Along with vasoconstriction, CAM possesses the capability to necrotize tissues and induce ischemia in organs leading to organ failure. Overlapping with the rise in COVID-19 cases, there was a surge of rhino-orbital-cerebral mucormycosis in those with active or recent COVID-19. MM has a high mortality even with the best of treatment. Review of existing literature shows that India contributed to 81% of the cases of COVID-19-associated ROCM.<sup>21</sup> COVID-19-associated rhino-orbital-cerebral mucormycosis (ROCM) has reached epidemic proportion during India's second wave of COVID-19 pandemic, with several risk factors being implicated in its pathogenesis. This study aimed to analyse the, and various modalities used to treat COVID-19 and the outcome of management.

### METHODOLOGY:

This was a retrospective, single-centre, observational study. The study was conducted in the Department of ENT at a tertiary care teaching institute of India. Between March 2021 and November 2021, our hospital treated 6418 COVID-19 confirmed patients. We observed a surge in mucor mycosis cases in May and June with 100 cases reported upto November. We planned to conduct this study to delineate the clinico-epidemiological profile of ROCM active or recent COVID-19 patients. Active COVID-19 cases were defined as patients who were laboratory confirmed for SARS-CoV2 by RT-PCR. Recent COVID-19 cases were had suffered from COVID-19 in the past 3 months of presentation, but currently SARS-CoV-2 negative. The time limit of 3 months was taken according to commonly accepted definition for post covid syndrome. ROCM was defined as patient with MM and acute or recent COVID-19 illness. The ethical approval was obtained from the Institute Ethics Committee before the commencement of the study.

### RESULTS

Demographic profile A total of 100 diagnosed ROCM were included

for the analysis. These patients presented to our department. 83 out of 100 patients (83%) were active COVID-19, whereas 17 patients (17%) were with recent COVID-19 infection (COVID-19 negative during presentation). The mean age of the included patients was 52.8 years, with an range of 36–82 years, with 70% males. Overall, a lag period was observed between the onset of COVID-19 symptoms and the onset of ROCM symptoms.

Only 1 out of 100 patients (1%) had no co morbidities, immunosuppressant use (including steroids) or recent blood glucose elevation. Majority of ve patients had underlying diabetes mellitus (n =63), of which were recently diagnosed during their COVID-19 illness. Eight patients (8%) had concomitant diabetic ketoacidosis. Following diabetes, the second most common comorbidity was hypertension (8%). Other comorbidities were present in 25% patients. Another common symptom was facial pain, which was the presenting complaint in 35% patients. Nearly 5% of patients presented with hemiplegia. 23 patients out of 100 patients presented to our department with unstable vital signs and triaged as 'Red' category (highest priority) as per institution protocol. The value of C-reactive protein was available for all 100 patients, 83% of them had values higher than 10 mg/l, with active inflammation due to COVID-19.

Diagnostic nasal endoscopy was performed for 79% of patients. For diagnostic evaluation, 43% had a deep nasal swab, while 48% samples were collected at sinus debridement. Microbiological evidence was available for 25 patients - direct microscopy with KOH/calcofluor white in 85% (22), smear in 5% (1), and culture in 10% (2) cases. At the time of analysis, histopathological confirmation was available for 35% patients. CT scan was done for 23% and MRI for 51%, while 12% underwent both CT and MRI. Diffuse PNS involvement was seen in 49% and bilateral PNS involvement was seen in 32%. In the orbit, diffuse involvement predominated in 31% followed by involvement of the medial orbit in 23%. Orbital apex was involved in 18% patients. In the CNS, cavernous sinus was most commonly involved in 12%. The categorization of the patients as per the proposed staging system for ROCM. Our study showed that 39% of the patients had disease severity stage 3b or less and 22% had stage 3c disease.

Management of COVID-19-associated ROCM: Primary initiation of medical management with amphotericin B was preferred in 78%, primary functional endoscopic sinus surgery (FESS)/PNS debridement was performed in 19% and both concurrently in 7%. Combination therapy with amphotericin B and posaconazole was provided in 19%. Of 100 patients for in our study, 71% were alive and well with regression of ROCM, 21% were alive with clinico-radiologically stable ROCM, 2% had progressive ROCM on treatment and rest 6% had expired.

### DISCUSSION:

We conducted a single-centre, retrospective study of 100 patients with

mucor. As the number of COVID associated mucormycosis cases were increasing in India during the second wave of COVID-19 pandemic, we have tried to delineate modality of management and outcome of patients.

In the Indian population, the mean age of COVID-19 patients admitted to a hospital was 45–50.7 years and 56–93% of the patients were males. In the reported cases of COVID-19-associated ROCM, there was a male predilection (79%). The demographic profile in our series was consistent with these studies with a mean age of 51.9 years and 71% male patients. Male gender has also been found to be associated with greater severity of COVID-19. Greater outdoor exposure and, therefore, to fungal spores may be the possible reason for this majority. 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>7</sup> described diabetes as a risk factor in 90% cases of which 52% had uncontrolled disease. Our study patients had prolonged use of corticosteroids increasing risk of MM has been reported in patients. Ribes et al described that acute or chronic use of steroids in such patients predisposed them to fungal infection.<sup>8</sup> 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. Our study had 79 patients who received steroid therapy.

Contrast-enhanced MRI is the imaging modality of choice. It allows delineation of soft tissue involvement earlier and is better than a CT scan, especially in the setting of orbital and cerebral involvement. Contrast-enhanced CT scan is relatively faster and can be used for patients where MRI is not feasible. In our study CT scan was done for 23% and MRI for 51%, while 12% underwent both CT and MRI

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. Diagnostic nasal endoscopy was performed for 79% of patients. For diagnostic evaluation, 43% had a deep nasal swab, while 48% samples were collected at sinus debridement. 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 analyzed. 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 hyperglycemia or any other risk factor, optimal surgical debridement, and medical management with antifungal agents. Amphotericin B is the antifungal drug of choice for mucormycosis. 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>10</sup> In our study, 19 % 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>11</sup> For cases associated with COVID-19, the overall mortality has been estimated to be 31%.<sup>12</sup> Results from our study show that overall, the mortality with COVID-19-associated ROCM is 6% and disease progression is seen in 21% of the cases. 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

COVID-19-associated ROCM predominantly affects middle aged and older males. Delayed presentation can occur up to three months. DM and corticosteroids are consistent, important, and independent risk factors for COVID-19-associated ROCM. Glycemic control is of paramount importance in a patient with COVID-19. Periorbital and facial pain and edema, nasal discharge, ptosis, and loss of vision are the common symptoms and signs. Contrast-enhanced MRI is the imaging modality of choice, in the absence of which a CT scan is suggested. ROCM should be staged, triaged, and managed by a team of different

specialties. Liposomal amphotericin B is the drug of choice and all efforts must be made to ensure its availability. PNS debridement should be radical and may be repeated as required. A longer follow-up is essential to determine the prognosis conclusively.

## REFERENCES:

1. Bogoch, I.I.; Watts, A.; Thomas-Bachli, A.; Huber, C.; Kraemer, M.U.G.; Khan, K. Pneumonia of unknown aetiology in Wuhan, China: Potential for international spread via commercial air travel. *J. Travel Med.* 2020, 27, taaa008.
2. Rothan, H.A.; Byrareddy, S.N. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J. Autoimmun.* 2020, 109, 102433.
3. WHO Coronavirus (COVID-19) Dashboard. WHO Coronavirus (COVID-19) Dashboard with Vaccination Data. Available online: <https://covid19.who.int/> (accessed on 23 May 2021).
4. Ye, Z.W.; Yuan, S.; Yuen, K.S.; Fung, S.Y.; Chan, C.P.; Jin, D.Y. Zoonotic origins of human coronaviruses. *Int. J. Biol. Sci.* 2020, 16, 1686–1697.
5. Mao, L.; Jin, H.; Wang, M.; Hu, Y.; Chen, S.; He, Q.; Chang, J.; Hong, C.; Zhou, Y.; Wang, D.; et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol.* 2020, 77, 683–690.
6. Yang, W.; Cao, Q.; Qin, L.; Wang, X.; Cheng, Z.; Pan, A.; Dai, J.; Sun, Q.; Zhao, F.; Qu, J.; et al. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): A multi-center study in Wenzhou city, Zhejiang, China. *J. Infect.* 2020, 80, 388–393.
7. Sharma S, Grover M, Bhargava S, Samdani S, Kataria T. Post coronavirus disease mucormycosis: a deadly addition to the pandemic spectrum. *J LARYNGOL Otol* 2021; 135:442–7
8. Ribes JA, Vanover-sams CL, Baker DJ. Zygomycetes in human disease. *Clin Microbiol Rev* 2000; 13:236–301
9. Hoenigl M, Seidel D, Carvalho A, Rudramurthy SM, Arastehfar A, Gangneux JP, et al. The Emergence of COVID-19 Associated Mucormycosis: Analysis of Cases From 18 Countries.
10. Manesh A, John A O, Mathew B, Varghese L, Rupa V, Zachariah A, et al. Posaconazole: An emerging therapeutic option for invasive rhino-orbito-cerebral mucormycosis. *Mycoses* 2016; 59:765-72.
11. Prakash H, Chakrabarti A. Epidemiology of mucormycosis in India. *Microorganisms* 2021;9:523
12. Singh AK, Singh R, Joshi SR, Misra A. Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India. *Diabetes Metab Syndr* 2021. doi: 10.1016/j.dsx.2021.05.019.