

## Rhino-orbital-cerebral mucormycosis: An epidemiological study from a tertiary care referral center in Western India

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**Purpose:** Rhino-orbital-cerebral mucormycosis (ROCM) is a rare opportunistic fungal infection with a fulminant course and an often fatal outcome. It can occur in immune-compromised patients such as those having uncontrolled diabetes, on long-term corticosteroid or immunosuppressive therapy, with COVID-19 infection, renal failure, AIDS, malignancy, or organ transplant. The aim of our study was to study the epidemiology of mucormycosis in COVID-19 patients and identify its risk factors. **Methods:** Ours was an epidemiological study wherein we gathered the demographic, clinical, histopathological, and radiological data of 458 patients of mucormycosis who presented to us between August 2020 and May 2021. Mucormycosis was defined through clinical and radiological findings or positive culture reports. **Results:** Out of all, 20.74% of patients did not have any past or concurrent history of COVID-19. The most common symptom of mucormycosis was orbital/facial pain (38.64%) and the most common sign was periorbital/facial edema (50.74%). Mucormycosis involving the nose and sinuses (94.54%) was most common followed by rhino-orbital (45.41%) and brain involvement (10.04%). The most common risk factor for mucormycosis was diabetes [81.92%], followed by corticosteroid use [79.69%] and supplemental oxygen [48.90%]. Most of the patients received similar treatment with IV amphotericin B [88.64%] and local debridement [80.74%]. **Conclusion:** With the third wave of COVID-19 still lurking, a fatal fungal infection should be kept in mind in COVID-19 active as well as recovered patients, especially those who have co-morbid medical conditions such as uncontrolled diabetes and who are treated with large doses of corticosteroids.

**Key words:** COVID-19, diabetes, fungal infection, opportunistic, rhino-orbital-cerebral mucormycosis

COVID-19 pandemic, an outbreak of coronavirus disease, was first identified in December 2019. The severity of the disease has been ranging from asymptomatic infection to respiratory failure and death.<sup>[1]</sup> Secondary fungal or bacterial infections or co-infections are important challenges, which increase the patients' morbidity and mortality.<sup>[1]</sup> Mucormycosis is currently a common fungal infection reported as a superinfection in COVID-19 patients.<sup>[2]</sup>

Zygomycetes comprises mucorales and entomophthorales. The former order causes life-threatening fungal infections such as mucormycosis mainly in immuno-compromised hosts, whereas the latter order causes superficial and mucocutaneous infections in immuno-competent hosts. Among the family of Mucoraceae, *Rhizopus oryzae* is the most common cause of infection.<sup>[3]</sup> Phagocytes are the major host defense mechanism against mucormycosis.<sup>[4,5]</sup> Systemic corticosteroid treatment affects the ability of these macrophages to prevent the germination of the fungal spores. The inappropriate use of corticosteroids for modulating immune-related lung injury and reducing the mortality rate in COVID-19 patients needing respiratory support and supplementary oxygen may predispose the patients to secondary infections, ultimately increasing the risk of mortality.<sup>[6]</sup> Uncontrolled diabetes mellitus is also the most common risk factor identified in patients with mucormycosis

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in COVID-19.<sup>[7]</sup> A hallmark of mucormycosis infection is the presence of extensive angioinvasion with resultant vessel thrombosis and tissue necrosis.<sup>[8]</sup> The infection can directly spread into the paranasal sinuses and then invade into orbital and intracranial spaces by direct spread or via the bloodstream.<sup>[8]</sup> This form is rhino-orbital-cerebral mucormycosis (ROCM) is the most common type of human mucormycosis.<sup>[6]</sup>

The second wave of COVID-19 disease has seen a surge in the incidence of invasive mucormycosis. We have come across hundreds of cases having varied presentations and outcomes. We conducted a study of ROCM in an attempt to study its epidemiology and risk factors. As per our knowledge, these data are the highest series reported from a single-center to date. With the possibility of further spikes of COVID-19, the study results may guide the prevention of another mucor epidemic.

### Methods

Ours is an epidemiological study wherein we report the details of 458 patients of mucormycosis who presented to us between

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August 2020 and May 2021 at our tertiary referral center, which is attached to a major COVID-19 hospital. The study was carried out maintaining patient confidentiality and in accordance with ethical standards and the Declarations of Helsinki.

The patients presented either with a concurrent or past history of COVID-19 infection along with clinical features of mucormycosis. The diagnosis of COVID-19 was based on the RT-PCR test of nasopharyngeal swabs. Proven mucormycosis was defined through clinical and radiological findings or positive culture reports. For all patients, we noted their demographic, clinical, histopathological, and radiological data. Based on clinical suspicion, a deep nasal swab was taken by the Otorhinolaryngology (ENT) department and sent for KOH (Potassium Hydroxide) mount and fungal culture. Magnetic resonance imaging (MRI) brain with orbit and paranasal sinus with/without CT scan was performed for assessing the extent of disease. Based on the radiological and nasal swab report, in conjunction with ENT and dental specialists, liposomal or deoxycholate amphotericin B was given intravenously with monitoring of renal parameters. Following clinical and radiological analysis, all patients were categorized into possible, probable, and proven ROCM.<sup>[9]</sup> Endoscopic sinus debridement was performed and specimens were sent for histopathology and microbiology assessment. Orbital exenteration was advised in patients with suboptimal response to systemic antifungal treatment and who had an intracranial extension and performed after stabilization of general condition.

**Results**

Our study included 458 patients of ROCM, 285 of which were males and 173 were females. In males as well as females, the maximum number of patients were in the age group of 45–59 years [Table 1]. The geographical distribution of the residence of the patients is shown in Fig. 1. The data regarding the possible risk factors for ROCM has been shared in Tables 2 and 3. Table 4 shows the clinical features of ROCM. The most common symptom of mucormycosis was orbital/facial pain (177 [38.64%] patients) and the most

common sign was periocular/facial edema (237 [50.74%] patients) [Figs. 2-4]. The mean duration of post-COVID-19 development of mucormycosis symptoms was 15.82 ± 11 days. The most common associations in decreasing order were steroid use 365 (90.35%), followed by diabetes 376 (81.92%), oxygen supplement 224 (62.22%), use of injection remdesivir 214 (52.71%), oral zinc supplement 151 (52.61%), regular steam inhalation 64 (28.19%), hypertension 95 (20.74%), and use of ayurvedic medications 43 (16.10%). Table 5 shows the diagnostic tests used for confirmation of diagnosis, Table 6

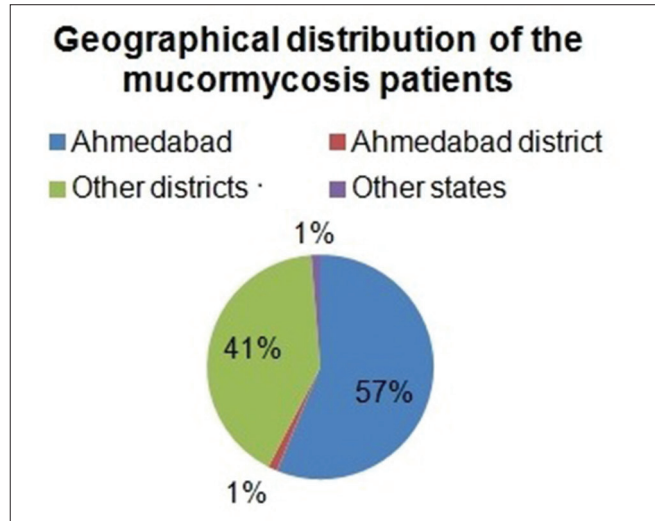


Figure 1: Geographical distribution of mucormycosis patients

**Table 1: Demographic data**

	Male	Female	Total (%)
Age (years)			
0-14	0	0	0
15-29	12	0	12 (2.62%)
30-44	60	37	97 (21.17%)
45-59	124	72	196 (42.79%)
60-74	82	51	133 (29.03%)
≥75	7	14	20 (4.36%)
Total	285	173	458 (100%)

**Table 2: History of COVID-19 infection**

History regarding COVID-19 infection	Yes	No
Past or present history of COVID-19 (n=458)	363 (79.26%)	95 (20.74%)
Hospital admission needed for COVID-19 (n=363)	308 (84.85%)	55 (15.15%)



Figure 2: Clinical photograph showing complete lid ptosis with proptosis and conjunctival chemosis



Figure 3: Clinical photograph showing corneal melting with a periorbital blackish scar

**Table 3: Risk factors**

Probable risk factor	Yes	No	Data not available
Co-morbidity			
Diabetes	376 (81.92%)	82 (17.90%)	-----
Hypertension	95 (20.74%)	363 (79.26%)	-----
Supplement oxygen taken	224 (62.22%)	136 (37.78%)	98 (21.39%)
History of steroid	365 (90.35%)	39 (9.65%)	54 (11.79%)
History of r emdesivir	214 (52.71%)	192 (47.29%)	52 (11.35%)
History of regular steam inhalation	64 (28.19%)	163 (71.81%)	231 (50.44%)
History of ayurvedic medication taken	43 (16.10%)	224 (83.90%)	191 (41.70%)
History of oral zinc supplement	151 (52.61%)	136 (47.39%)	171 (37.34%)

**Table 4: Clinical features**

Presenting symptoms	No. of patients (n=458)	Presenting signs	No. of patients (n=458)
Orbital/facial pain	177 (38.64%)	Periocular/facial edema	237 (51.74%)
Orbital/facial edema	131 (28.60%)	Ptosis	53 (11.57%)
Nasal block	41 (8.95%)	Nasal discharge	47 (10.26%)
Ptosis	38 (8.29%)	Periocular hypoesthesia	15 (3.27%)
Nasal discharge	34 (7.42%)	Periocular/facial discoloration	07 (1.52%)
Loss of vision	07 (1.52%)	Loss of vision	07 (1.52%)
Proptosis	04 (0.87%)	Proptosis	04 (0.87%)
Diplopia	02 (0.43%)	Diplopia	02 (0.43%)
Orbital/facial discoloration	02 (0.43%)	Nasal ulcer/eschar	02 (0.43%)

**Table 5: Microbiological tests for confirmation of diagnosis**

Confirmation of diagnosis (microbiological)	No. of patients*
KOH	375 (89.50%)
Smear	17 (4.06%)
Culture	27 (6.44%)
Total	419

\*For 39 patients, data were not available

**Table 6: Organ involvement**

Organ involvement	No. of patients
Nasal cavity	44 (9.60%)
PNS involvement	
389 (84.93%)	Unilateral 187 (48.07%) Bilateral 202 (51.93%)
Orbit	
208 (45.41%)	Unilateral 173 (83.17%) Bilateral 35 (16.83%)
Brain	46 (10.04%)

shows organ involvement, Table 7 shows ROCM staging,<sup>[9]</sup> and Table 8 shows definitive treatment of patients.

## Discussion

Mucormycosis is an acute and potentially fatal fungal infection caused by fungi related to the Mucoraceae family.<sup>[10]</sup> These fungi are opportunist organisms and can be found in fruit, soil, feces and may be cultured from the nasal and oral mucosa of healthy humans.<sup>[10]</sup> The pathogen as an asexual spore-forming fungus can infect the oral and nasal cavities through inhalation. In the presence of a normal immune system, the spores are removed

by phagocytic leukocytes.<sup>[10]</sup> The pathogen can transform into hyphae form in individuals with predisposing factors such as uncontrolled diabetes (particularly in the presence of ketoacidosis), malignancy (such as lymphoma and leukemia), renal failure, organ transplantation, advanced rheumatologic disorders using immunosuppressive agents (e.g., prolonged use of corticosteroids), AIDS, extensive burns, and chronic sinusitis.<sup>[11]</sup> In these conditions, leukocytes have less efficacy on the hyphae forms of fungi and the pathogen may proliferate more easily.<sup>[10]</sup> The organism proliferates and invades the vessel walls of the infected region, resulting in thrombosis, ischemia, and necrosis.<sup>[10]</sup> It can directly spread into the paranasal sinuses and invade into orbital and intracranial spaces.<sup>[8]</sup> The symptoms presenting in ROCM are facial pain and paresthesia, headache, periorbital and nasal swelling, inflammation, eyelid drooping, proptosis, external and internal ophthalmoplegia, visual loss, and blackish necrosis of palate and nasal mucosa. The disease usually starts from the nasal and oral mucosa, spreads to the paranasal sinuses, and advances into the orbital space through the lamina papyracea. Vision loss may occur due to the involvement of the optic nerve or vessels supplying the retina. The intracranial space can be involved either directly through the orbital orifices and sinus walls or blood. Cavernous sinus thrombosis as another complication results in damage to the cranial nerves III, IV, VI, V2, and VI.<sup>[12]</sup> Regular examination and imaging (CT and MRI) are crucial to detect the propagation of the mucormycosis.<sup>[6]</sup> Based on the infected region, the imaging findings may include opacification of involved paranasal sinuses, bone destruction of sinus walls, alterations of intraorbital tissue signal with or without focal mass, cavernous sinus filling defect, intracranial focal mass, and/or alteration of the meningeal signal.<sup>[10,11]</sup>





**Figure 4:** Clinical photograph of the right eye showing total ophthalmoplegia

**Table 7: ROCM grading<sup>[9]</sup>**

Stage of ROCM at diagnosis	1	2	3	4
No. of patients (n=458)	44 (9.61%)	199 (43.45%)	169 (36.90%)	46 (10.04%)

**Table 8: Primary definitive treatment for ROCM**

Primary management	No. of patients
Amphotericin B	406 (88.64%)
Posaconazole	22 (4.80%)
Isavuconazole	0
Functional endoscopic sinus surgery (FESS)	370 (80.78%)
Exenteration	19 (4.14%)

ROCM is a relatively fatal infection and in cases of brain involvement, mortality rises to 50%–85%.<sup>[13]</sup> Survival depends on timely diagnosis, alleviation of predisposing factors, aggressive debridement of necrotic tissues, and appropriate systemic antifungal therapy.<sup>[10]</sup> Predisposing factors such as corticosteroid therapy should be discontinued, and blood sugar should be controlled restrictively. Systemic amphotericin B and its liposomal formulation are the first drug of choice for the treatment of mucormycosis and significantly improve the survival rate.<sup>[13]</sup> Posaconazole is an oral antifungal used as step-down therapy after initial treatment by amphotericin B.<sup>[11]</sup> Regular daily debridement of necrotic tissues from paranasal sinuses is necessary to prevent the propagation of mucormycosis.<sup>[8]</sup> Irrigation of the sinuses and the involved regions with diluted amphotericin B has also been recommended.<sup>[10]</sup> Orbital exenteration may be done in the presence of widespread necrosis.

The Collaborative Oculoplasty Association of India, Indian Journal of Ophthalmology (OPAI-IJO) Study on mucormycosis in COVID-19 (COSMIC), report one published

data of 2,826 patients of COVID-19-associated ROCM from all over India.<sup>[14]</sup> In their report, the mean duration of symptoms of ROCM was between days 10 and 15 from the diagnosis of COVID-19. Fifty-seven percent of the patients needed oxygen support for COVID-19 infection, 87% were treated with corticosteroids, (21% for > 10 days), and diabetes mellitus (DM) was present in 78% of patients. In our study, the mean duration of post-COVID-19 development of mucormycosis symptoms was between days 5 and 25, steroid use was noted in 79.69% and the need for oxygen supplement was seen in 48.90%. Study of COVID-19-associated mucormycosis from western India by Shweta Walia *et al.*<sup>[15]</sup> reported 540 proven cases of mucormycosis. In their study also, the most common presentation was periocular and facial swelling. Ninety-seven percent of the patients had associated diabetes, 89.44% of patients had a history of COVID-19 along with a concurrent history of steroid use. An association with the use of higher antibiotics (82.59%), oxygen therapy (52.40%), and injection remdesivir (28.89%) was also noted. Another study reported by Ajay *et al.*<sup>[16]</sup> included 67 cases of COVID-19-associated mucormycosis. In their study also, uncontrolled diabetes (90%) with ketoacidosis (40%) and the use of systemic steroids (84%) were strong predisposing factors. A case series of invasive mucormycosis in patients with COVID-19 infection published by Mishra *et al.*<sup>[17]</sup> reported 10 cases of mucormycosis in COVID-19 or post-COVID-19 patients. In their study, nine patients underwent functional endoscopic sinus surgery (FESS) with local debridement and six patients were advised exenteration; however, unfortunately, two patients succumbed to COVID-19 and four did not give consent for the same. Another case report published by Veisi *et al.*<sup>[12]</sup> concluded that

patients undergoing corticosteroid therapy for COVID-19 have a higher risk of rhino-orbital and/or rhino-orbito-cerebral mucor, particularly when another risk factor such as diabetes is present. In our series also, 53 patients had prior or COVID-19 precipitated diabetes. A study published by Song *et al.*<sup>[13]</sup> investigated 99 patients of fungal infections post-COVID-19 in China and found out that about 5% of these were due to *Aspergillus* and 7% due to *Mucor* species. They concluded that the impairment of T-cell immunity along with the presence of an underlying immune-compromised state is one of the most important pathogenesis.<sup>[6]</sup> In a case report published by Mehta *et al.*<sup>[18]</sup> reported a case of post-COVID-19 ROCM in which the patient received steroids following the protocols, after which he developed mucormycosis. According to their hypothesis, it could be due to the alterations in the immunity, especially T cells and innate immunity, and the use of steroids could be the cause of invasive fungal infection post-COVID-19.<sup>[8]</sup> Similar observations have been reported by Werthman–Ehrenreich *et al.* and Chowdhary *et al.*<sup>[19,20]</sup>

Our center being a tertiary referral hospital, the patients presented to us may be exhibiting varying clinical manifestations and could be at varying stages of the disease. Also, they may not necessarily have been treatment-naïve patients. In spite of these limitations, these data reflect the incidence and severity of this disease and the common risk factors for the same.

## Conclusion

From our study, it is apparent that patients with COVID-19 infection are susceptible to mucormycosis because of impairment of barrier defense, dysfunction of phagocytes and lymphocytes, and the use of immunosuppressive medications such as steroids. COVID-19 patients undergoing corticosteroid therapy have a higher risk of rhino-orbital and/or rhino-orbito-cerebral mucormycosis, particularly when another risk factor such as diabetes is present. Other risk factor associations noted were oxygen supplement, use of injection remdesivir, oral zinc supplement, regular steam inhalation, hypertension, and the use of ayurvedic medications. In such susceptible patients, vigilant monitoring for the onset of symptoms is crucial. Early diagnosis and treatment of secondary fungal infections with nasal debridement, antifungals, and exenteration can substantially reduce morbidity and mortality.

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## Conflicts of interest

There are no conflicts of interest.

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