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**Case Series**

# A menace to human health: rhino-orbital cerebral mucormycosis

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## ABSTRACT

Collate and interpret data on rhino-orbital-cerebral mucormycosis (ROCM) infections admitted at the tertiary care centre and investigate the common contributing factors leading to such infections and highlighting the relationship of this upsurge seen in patients infected with COVID-19. We conducted a cross-sectional study in Central India, in the period of eleven days (from 9 May to 18 May). A total of ten patients with ROCM was investigated, admitted to the separate ward for mucormycosis in the tertiary care centre. A self-pre-designed questionnaire was used for the evaluation. Verbal consent was obtained from the patients before the start of the study and also ensured the confidentiality of their respective details. Among ten of the patients, six patients were known cases of diabetes mellitus, two of the patients were diagnosed with diabetes mellitus after the initiation of corticosteroid therapy during their treatment and two of them were non-diabetic. All the patients in this case series were on corticosteroid therapy and on oxygen supplementation. Majority of the patients showing mild to moderate disease with unilateral symptoms, although only 10% showed the severe disease with bilateral eye involvement. It is evident that the poor or impaired immune functioning is the leading cause of the upsurge in mucormycosis cases. Therefore, early diagnosis and treatment of fungal infections can substantially reduce morbidity and mortality.

**Keywords:** Mucormycosis, COVID-19, Diabetes mellitus, Corticosteroid, Amphotericin B, Rhino-orbital-cerebral mucormycosis

## INTRODUCTION

The mucor species incudes *Rhizopus*, *Absidia* and *Cunninghamella* are the leading causative agent for mucormycosis in humans.[1] Mucormycosis mainly infects the sinuses, brain or lungs.[2] Zygomycosis and Mucormycoses occur in soil and their airborne spores often contaminate food and laboratory specimens and enhance infections.[3] Thrombosis and tissue necrosis are the key symptoms in fungal infection and do require antifungal drug therapy and surgical intervention.[4] Mucormycosis is a rare but severe invasive fungal infection, mainly occurring in immune-compromised patients, especially in patients diagnosed with uncontrolled diabetes mellitus specifically with diabetic ketoacidosis or blood malignancies. Also includes chronic neutropenia, intravenous drug users, malnourished individuals, organ transplantation, prolonged hospital stay and severe skin damages.[5-9]

The rhino-orbital presentation is very frequent concurrent COVID-19. Patients with coronavirus disease (COVID-19) can be associated to significant and sustained lymphopenia compromising the immune system, especially in the most severe cases, susceptible to develop invasive mycosis.[8] The diagnosis is often made late, especially for some patients presenting with atypical features initially such as headache, swelling of the eyelids

and cheeks and nasal stuffiness. Mucormycosis has proven to be fatal if not recognized and treated promptly. We hereby, presented a case series of ten patients with typical features of ROCM for the evaluation of the risk factors associated with invasive mycosis.

## CASE SERIES

We conducted a cross-sectional study in Central India, in the period of eleven days (from 9 May to 18 May). A total of ten patients with ROCM was investigated, admitted to the separate ward for invasive mycosis in the hospital. The mean age of the patients was 56.6 years (±8.003). Majority of the patients belongs to 51-60 age group with 50% (N=5), and 20% to 40-50 age-group (N=2). Whereas 80% of the male involvement was present (N=8), and 20% of females (N=2). A self-pre-designed questionnaire was used for the evaluation, which included socio-demographic profile, covid history, any co-morbidity, any specific drug administration, clinical signs and radiological investigations. Verbal consent was obtained from each patient before conduction of this study and also ensured the confidentiality of their respective details.

The diagnosis of mucormycosis was made by histological examination, CT and MRI in all patients. Treatment with systemic amphotericin B was started as soon as the diagnosis of mucormycosis was established to every patient and surgical debridement was indicated in the required one.

Table 1 shows the socio-demographic characteristics and clinical details of the patients, radiological evidence and the treatment details associated with COVID-19. Out of the cases of ROCM treated in our hospital, eight were male and two were females. Diabetes, corticosteroid therapy, oxygen supplementation was the most likely risk factor, presenting in eight patients. One patient presented with chronic kidney diseases plus hypertension and diabetes mellitus and one of the patients was on an immunomodulator. All ten patients received steroids for covid treatment and eight were diabetic (of whom six patients who were diabetics received steroids for COVID-19 treatment). There was an evidence of eye involvement in six patients, whereas four of them were not. The vision was altered in another one patient only and others were presented with the typical symptoms of invasive mycosis. All the patients underdone radiological investigations and went through adequate treatment they required.

Table 2 revealed presentation of the typical symptoms associated with mucormycosis. Maximum patients were blown out with headache (25%), followed by swelling in eyes (14.3%), redness in eyes (10.7%), whereas few of them were complaining of pain in eyes and jaw, swelling in nose, watering in eyes and least of with other symptom. Hence, 90% of the patients showing unilateral symptoms, whereas only 10% of them shows bilateral features.

**Figure 1: Clinical picture showing proptosed eyeball with discharge, matted eyelashes, conjunctival congestion, chemosis and exposure keratopathy of the right eye.**

**Figure 2: Clinical picture showing crusting present over upper and lower lid, and at maxillary area, lid swelling and ptosis.**

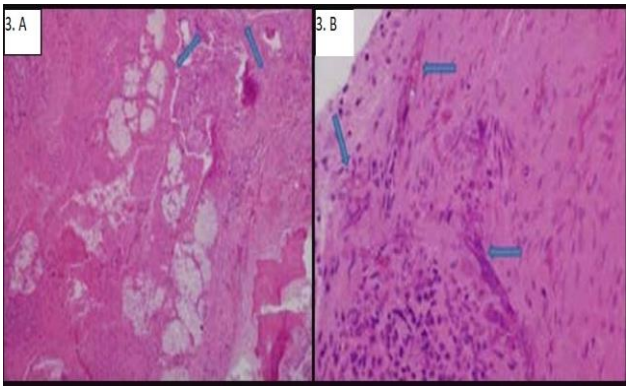


**Figure 3: Histopathology. (A) lower power view of fungal sinusitis with excessive tissue necrosis; rare mucor organisms (arrows can be seen); (B) mucorales organism (arrows) can be seen invading connective tissue.**

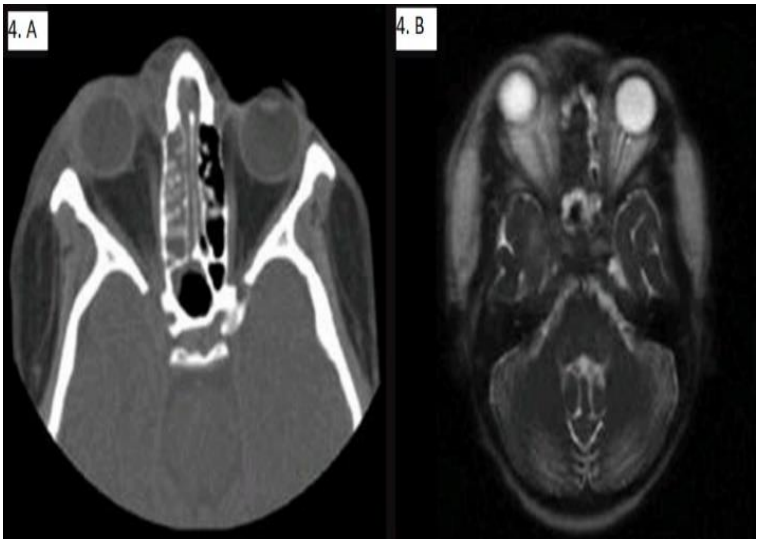


**Figure 4: Orbital imaging; (A) CT of the orbits showing opacification of the right paranasal sinus; (B) MRI demonstrates correlating nonenhancement of the right nasal sinus mucosa.**

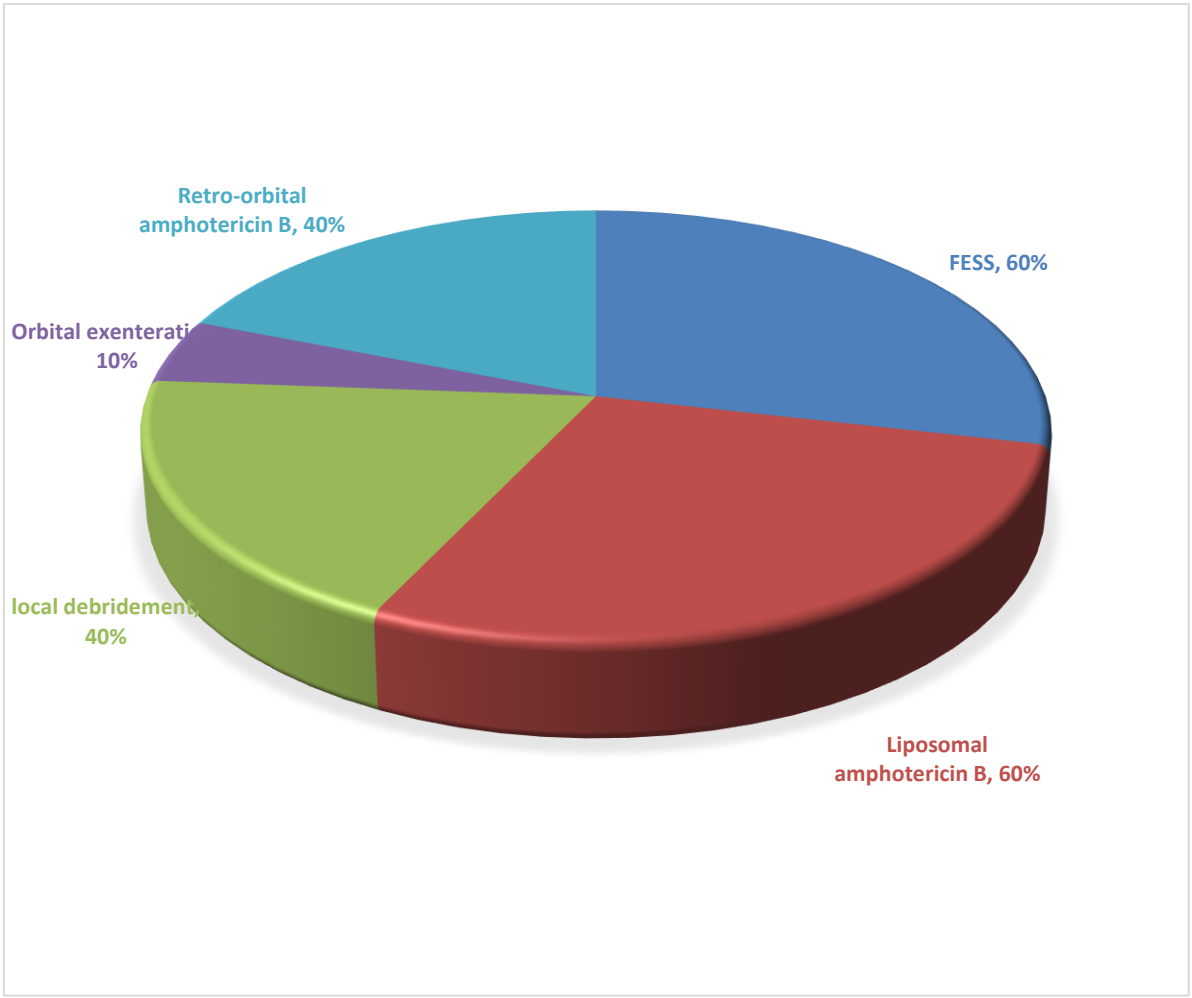


**Figure 5: Illustrated the treatment of the patients for the mucormycosis they underwent; maximum patients were gone through fess and liposomal amphotericin b, few of them received local debridement and retro-orbital amphotericin b and only one of them got orbital exenteration.**

**Table 1: Demographics and clinical details of the patients with mucormycosis.**

| S. no. | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| **Age (in years)** | 48 | 52 | 55 | 52 | 53 | 50 | 70 | 64 | 53 | 69 |
| **Sex** | Male | Female | Male | Male | Male | Male | Male | Female | Male | Male |
| **Comorbidities** | Nil | DM type 2 | DM type 2 | DM type 2 | DM type 2 | DM type 2 | DM type 2, CKD, hypertension | Nil | DM type 2 | DM type 2 |
| **Severity** | Severe | Severe | Severe | Severe | Severe | Severe | Severe | Moderate | Moderate | Severe |
| **Steroids** | Injectables | Injectables | Injectables | Injectables | Injectables | Injectables | Injectables | Oral | Injectables | Injectables |
| **Antiviral/immunomodulator** | Remdesivir | No | Remdesivir | Tocilizumab | Remdesivir | Remdesivir | Remdesivir | No | No | Remdesivir |
| **O2 requirement and duration** | Yes 24 days | Yes 20 days | Yes 15 days | Yes 17 days | Yes 16 days | Yes 15 days | Yes 26 days | Yes 20 days | Yes 15 days | Yes 16 days |
| **Clinical presentation** | Headache, swelling in nose | Headache, swelling in right cheek and rt nostril | Headache, pain in left cheek and nose | Right side facial swelling, pain in jaw | Headache, swelling and pain in left eye | Headache, swelling and pain in right eye | Headache, loss of vision in both eyes, watering and redness in eyes | Nasal bleeding, swelling in left eye and left side of face | Headache, swelling and redness in right eye | Redness and watering in left eye, hardening of nose |
| **Eye involvement** | Nil | Nil | Nil | Nil | Left eye | Right eye | Both eyes | Left eye | Right eye | Left eye |
| **HPE and fungal smear (broad aseptate hyphae/angioinvasion)** | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| **Treatment** | FESS and local debridement and liposomal amphotericin B | FESS and local debridement and liposomal amphotericin B | FESS and local debridement and liposomal amphotericin B | FESS and local debridement and liposomal amphotericin B | Retro-orbital amphotericin B, symptomatic management | Retro-orbital amphotericin B, symptomatic management | Orbital exenteration and debridement of fungal sinusitis liposomal amphotericin B | FESS and local debridement, liposomal amphotericin B | Retro-orbital amphotericin B, symptomatic management | FESS, retro-orbital amphotericin B |
| **Radiological evidence** | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

DM-diabetes mellitus, FESS-functional endoscopic sinus surgery, CKD-chronic kidney disease, HPE-histopathological examination

**Table 2: Presentation of symptoms in patients with mucormycosis.**

| Symptoms | % |
|---|---|
| **Facial swelling** | 10.0 |
| **Hardening of nose** | 10.0 |
| **Headache** | 70.0 |
| **Loss of vision in both eyes** | 10.0 |
| **Nasal bleeding** | 10.0 |
| **Pain in eyes** | 20.0 |
| **Pain in jaw** | 20.0 |
| **Pain in nose** | 10.0 |
| **Redness in eyes** | 30.0 |
| **Swelling in cheek** | 10.0 |
| **Swelling in eyes** | 40.0 |
| **Swelling in nose** | 20.0 |
| **Watering in eyes** | 20.0 |

## DISCUSSION

Our case series highlights the possibility of a correlation between COVID-19 and mucormycosis infection. Pathogenesis of mucormycosis states that mononuclear and polymorphonuclear phagocytes of normal hosts kill mucorales by generation of oxidative metabolites and defensins, hence risk of development of invasive mucormycosis occurs in neutropenic patients and those with dysfunctional phagocytes, hence making the patient more susceptible to systemic fungal infections.[9-12]

In our study, patients usually presented with headache (70%), eye swelling (40%), redness in eyes (30%), watering eyes (20%), jaw pain (20%), pain in the eyes (20%), swelling in nose (20%). However, cases of facial swelling, hardening nose, loss of vision in both eyes, nasal bleed, pain in nose and swelling in nose are relatively less and can be found in approximately 10% of patients with ROCM. Majority of the patients showing mild to moderate disease with unilateral symptoms, although only 10% showed the severe disease with bilateral eye involvement. On the other hand, longer duration of oxygen requirement in the COVID-19 patients recommend prolonged staying in the hospital or ICU, which was vitalized to develop mucor infection in this series. Furthermore, with the same discoveries, a study published by Soumya et al and Moorthy et al reported that, 67% of the patients were presented with the complain of headache, 67% with the loss of vision, which is contrary to this study and 30% were with nasal symptoms.[6,7] Precedingly, another scholar Zilberberg et al also stated the related finding that longer duration of staying in the hospital played substantial role in developing mucormycosis infection.[9]

The hallmark recovery of this series emphasized the use of steroids in reducing the need of invasive ventilation in hypoxic patients and the hospital stay and ultimately decreasing the mortality. Administration of prolonged steroids results in a neutrophilic leucocytosis and the impaired ability of leukocytes to migrate to the site of inflammation due to its inhibitory effects on cytokines and chemokines leads to many opportunistic infections.[12] Recent published evidence says that COVID-19 is a pro-coagulable state and there is increased incidence of thrombotic events.[13] Due to vessel thrombosis this pro-coagulable state provides a clear pathway for the angioinvasion of mucor and leading to disseminated infections. The impairment of T cell immunity along with pre-existing immunocompromised state is one of the most important pathogenesis in their conclusion.[12] In a case report published by Mehta et al where they have reported a case of post COVID-19 rhino-orbital mucormycosis concluded that it may be due to the alterations in the immunity especially T cells and innate immunity and the excessive use of steroids may be the cause of invasive fungal infection in the post-covid duration.[14] Similar observations have been reported in studies done by Amanda et al and Chaudhary et al conducted in America and New Delhi respectively.[15,16]

The relationship between mucor infection and diabetes is well established. Uncontrolled diabetes creates environs for infections and wreck glycaemic homeostasis.[17] People with type 2 diabetes are at galloping pace, but more than 80% reside in low and middle-income countries such as India, Bangladesh, Bhutan, Pakistan, Sri Lanka, the Philippines and Indonesia. Amongst the top 10 countries in the world, India stands second with 77 million people with diabetes and another 36.5 million with prediabetes.[18] In the present study, around 80% of the patients found to have diabetes to contract the infection. Exceedingly, diabetic keto-acidosis also disrupts iron binding of transferrin, resulting in increased proportion of unbound iron, which may promote growth of the fungus.[19,20] The association of mucormycosis with uncontrolled diabetes is proved and it is known to be an infection specific to diabetics, although rarely seen in the normal population.[17,21] COVID-19 infection can worsen diabetes control and some treatments used for COVID treatment

(e.g. steroids/tocilizumab) can exacerbate hyperglycaemia.[17]

It is easy to interpret from the above discussion that the increased incidence of mucormycosis is not only caused by COVID-19 infection, diabetes and steroid administration independently, despite this trio arouse this havoc and has self-potentiated the problem of immune dysregulation leading to fungal invasion. Our limited but significant numbers of diabetics and steroid administration come to prove this very hypothesis.

## CONCLUSION

We concluded that COVID-19 patients are more prone to mucormycosis because of imbalance of phagocytes and lymphocytes, impairment of defence mechanism and the use of immunosuppressive medications. Treating clinicians need to be aware of the possibility of mucormycosis, in such patients particularly in those with underlying comorbidities. Early diagnosis and treatment of fungal infections can substantially reduce morbidity and mortality.

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