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Resurgence of orbital mucormycosis during COVID-19 pandemic: Study from a tertiary care center in Eastern India

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Abstract:

PURPOSE: A sudden surge of Mucormycosis cases during the second wave of Covid 19 was observed in certain parts of India. The reasons for this upsurge remain unknown. However its impact on the overall healthcare system was quite overwhelming. In this context this study was decided to estimate and assess the spectrum of orbital involvement in patients with Mucormycosis, to find its association with coexisting disease entities if any, and at the same time evaluate the therapeutic response to established treatment regimens.

MATERIALS AND METHODS: This descriptive longitudinal study was conducted over a period of six months. Patients presenting with symptoms of Mucormycosis were jointly evaluated by a multi speciality team. After confirmation of diagnosis, patients were treated with intravenous Amphotericin B, surgical debridement of affected sinuses and orbital exenteration when indicated. They were followed up for three months after discharge.

RESULTS: Forty-three patients were enrolled in this study. Thirty-seven (86.04%) were COVID positive. All of them had history of steroid exposure during COVID treatment. Ninety five percent of study participants had diabetes mellitus. Twenty-seven (62.79%) patients had orbital involvement. Most common clinical presentation was peri-orbital or facial pain and edema. Besides medical treatment, thirty-nine patients (90.69%) required sinus debridement and nine patients (20.9%) required orbital exenteration. Thirteen patients (30.23%) expired during the follow up period. With treatment disease regressed in twenty patients (46.51%).

CONCLUSION: Diabetes and use of steroids to prevent anticipated cytokine storm may be the inciting factors for Orbital Mucormycosis in COVID patients. Early diagnosis, treatment and control of risk factors are keys for recovery and survival..

Keywords:

Amphotericin B, COVID, hyperglycemia, orbital mucormycosis

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Introduction

Mucormycosis is an opportunistic fungal infection that usually affects patients whose immune status is compromised for any reason. Diabetes mellitus has been found to be the most common predisposing factor and was present in around 50%–71% of all the cases of mucormycosis reported worldwide.[1]

The most common mode of transmission of these fungi is through inhalation of fungal spores or conidia. The two other modes of spread are traumatic inoculation into the skin or nasal mucosa and through ingestion.[2] Once these spores enter the tissues, they find their way into the blood vessels and get lodged into them. It forms a thrombus, which leads to occlusion of blood supply to the affected tissues, thereby causing ischemic necrosis. The necrosis is responsible for

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the blackening of the tissues, which is the hallmark of mucormycosis infection[3] and is also the reason for its colloquial name "black fungus." From paranasal sinuses, it can proceed to involve orbit, leading to the destruction of orbital contents, thereby causing profound visual loss. Finally, it may spread intracranially, becoming more complex and causing a prognostically poorer outcome. This type of mucormycosis has also been referred to as rhino-orbito-cerebral mucormycosis (ROCM).

The management of orbital mucormycosis is surgical debridement of all the necrosed tissue along with injection amphotericin B (1 mg/kg/day, for 4 weeks) and step-down therapy with oral Posaconazole 300 mg OD on day 1 followed by 300 mg BD for 3 months. When the orbit is involved, all efforts should be made to preserve the eye and defer a destructive procedure like exenteration as long as possible.[4]

There was a sudden surge of mucormycosis cases in India during the second wave of the COVID-19 pandemic, extending from March to July 2021. The exact reason for this surge remains unknown. Furthermore, not all patients encountered during this period were immunocompromised. A need, therefore, was felt for further documentation and research.

Aims and objectives

The aim of this study was threefold: first, to assess the extent and spectrum of orbital involvement among patients presenting with mucormycosis; second, to evaluate the association of COVID-19 or any other comorbidity with mucormycosis; and finally, to evaluate the therapeutic response of orbital mucormycosis to established protocols of treatment.

Materials and Methods

This descriptive longitudinal study was conducted for 6 months from April to October 2021 at a regional tertiary care center in Eastern India after it was approved by the institutional ethics committee (vide memo no. BSMC/aca/3623 dated December 7, 2021). It was declared as a regional center for mucormycosis management during the second wave of the COVID-19 pandemic. Required permission was obtained from the institutional ethical committee before the commencement of the study. Only patients who voluntarily agreed to be a part of this study were included and mandated to sign an informed consent form.

The sample size was not predecided. As mucormycosis is a rare disease and during COVID-19 times, the unprecedented rise of COVID-19 cases enforced authors to conduct the study. Any patient attending any outpatients' unit with complaints and clinical features suggestive of mucormycosis was pooled into a "Mucormycosis Clinic" which comprised faculty members from the departments of ophthalmology, otorhinolaryngology, general medicine, radiology, and pathology. Diagnosis was then confirmed by radiology (computed tomography [CT] or magnetic resonance imaging [MRI] scan) and histopathological examination. A total of 43 patients were diagnosed with mucormycosis during this period. All of them consented and were included in this study.

We have followed the proposed classification of Honavar[5] for staging the mucormycosis cases. They were also managed according to the management algorithm published by Honavar.[5] Intravenous liposomal amphotericin B (5–10 mg/kg) was given for 30 days, followed by oral posaconazole 300 mg OD on day 1, followed by 300 mg BD for 90 days. During the course of treatment, many patients required surgical intervention. In all cases of orbital and ophthalmic involvement, patients were monitored until the final outcome or up to 3 months, whichever was later.

Data were analyzed using the standard statistical tests using MS Excel software, 2019 version, (Microsoft Corporation, US, www.office.com).

Results

Of 43 patients, 26 were males (60%) and 17 were females (40%). Mean age was 50.04 years (standard deviation [SD] ±12.29). Among the comorbidities present, 41 patients (95%) had diabetes. Fifteen had uncontrolled diabetes (36%) and three (7%) had diabetic ketoacidosis (DKA).

Table 1: The distribution of study participants according to proposed staging classification (*n*=43)

Stage	Number of patients (%)
1A	1 (2.32)
1B	0
1C	0
1D	0
2A	3 (6.97)
2B	4 (9.30)
2C	7 (16.27)
2D	1 (2.32)
3A	4 (9.30)
3B	2 (4.65)
3C	7 (16.27)
3D	0
4A	3 (6.97)
4B	1 (2.32)
4C	8 (18.60)
4D	2 (4.65)
Total	43 (100)

Table 2: Pattern of orbit involvement of study participants (*n*=43)

Orbit involvement	Number of patients (%)
Medial orbit	5 (11.6)
Inferior orbit	2 (4.65)
Apex	5 (11.62)
Diffuse	14 (32.55)
Medial and inferior orbit	1 (2.32)
Total orbital involvement	27 (62.79)

Table 3: Profile of death patients (*n*=13)

Stage	Co-morbidities	Remarks
3C	Uncontrolled DM	Exenterated
3A	Uncontrolled DM	
4C	DKA	
2D	DKA	
4A	Uncontrolled DM	Unfit for exenteration
4C	Controlled DM with insulin CKD under dialysis	Unfit for exenteration
4C	Controlled DM with insulin	Unfit for exenteration
4C	Uncontrolled DM	Unfit for exenteration
4D	Controlled with insulin	Unfit for exenteration
4B	Uncontrolled	Unfit for exenteration
4A	Controlled with insulin	Unfit for exenteration
4A	Uncontrolled	Unfit for exenteration
2C	Uncontrolled and CKD	Death during hemodialysis

CKD=Chronic kidney disease, DM=Diabetes mellitus, DKA=Diabetic ketoacidosis

Of the 43 patients, 37 (90%) were reverse transcription-polymerase chain reaction (RT PCR) positive for COVID-19. Patients developed symptoms suggestive of mucormycosis after an average of 25.08 ± 18.70 days from the detection of COVID-19. All COVID-19-positive study participants had a history of steroid therapy. Twelve patients (22%) had been treated with oral steroids (prednisolone 1 mg/kg body weight) for an average 7.84 days. Twenty-nine (78%) patients had been treated with intravenous steroids (dexamethasone 1% w/v) for an average duration of 6 days during their COVID-19 treatment. Four patients received both oral and intravenous steroids during their COVID-19 treatment.

After confirmation of diagnosis, patients were classified into stages for orbital mucormycosis, as shown in Table 1. Twenty-eight patients (65%) had orbital involvement and thirteen (30%) had central nervous system (CNS) involvement [Table 2]. Among the patients with orbital involvement, diffuse orbital lesion (14 patients, 32.5%) was the most common finding, followed by medial orbit involvement (five patients, 11.6%). There was almost an equal share of involvement between the right and left sides. Only one patient had bilateral orbital involvement.

The most common clinical presentation was periorbital or facial pain (35 patients, 81%) and periorbital or facial

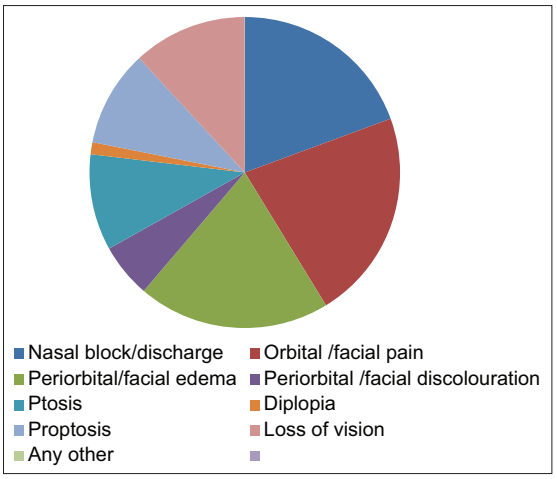

Figure 1: Distribution of patients according to their various presentations (*n* = 43)

edema (32 patients, 72.41%). Details of presenting signs and symptoms are given in Figure 1. Twenty patients (46.5%) complained about the dimness of vision. Optic nerve compression was found to be the most common cause of dimness of vision (17 patients, 39.5%). This was inferred clinically by the presence of a relative afferent pupillary defect and substantiated by CT or MRI scans showing evidence of optic nerve involvement. Ophthalmoplegia was found in 26 (60.4%) patients. The most common cause of ophthalmoplegia was isolated or combined palsy of III, IV, and VI cranial nerves (15 out of 26 patients, 57.6%). Nine patients (20.9%) had trigeminal nerve involvement, whereas two (4.6%) had both trigeminal and facial nerve involvement. Twenty (51.16%) patients presented with ptosis and 16 (37.2%) had proptosis. Out of proptosis cases, 10 (62.5%) had 2 ml proptosis, whereas six (37.5%) had 3 ml or more of proptosis.

The average duration of hospitalization was 26.52 days (SD ± 13.14). Thirty-nine patients (90.69%) required sinus debridement. More than half of them (20 patients, 51.2%) required debridement of all the paranasal sinuses (maxilla, ethmoid, frontal, and sphenoid). After thorough debridement of sinuses, the surgical field was irrigated with amphotericin B in all cases. Retrobulbar amphotericin B (3.5 mg/mL) was given to 22 (56.4%) patients. Retrobulbar amphotericin B injection was given ranging from minimum one to maximum three per patients with a mean number of injections 1.9 (SD ± 0.52). Orbital exenteration was performed in nine patients (23.0%).

The details of patients died during the course of treatment, depicted in Table 3 with their clinical staging of the disease and associated co-morbidities. During the course of follow-up, 13 patients expired, making the case fatality rate 30.2%. This included one patient who had already undergone exenteration for orbital involvement.

Of the remaining 30 patients, 7 (16.2%) had to undergo exenteration of the affected orbit, leaving no scope of visual reinstation. Of the rest, 20 (46.5%) patients had visual acuity ranging between 6/9 and 6/18. One patient had a visual acuity of 6/60 and one inaccurate perception of light. Both these patients had evidence of optic nerve compression on neuroradiology, which did not resolve following therapy.

Discussion

The upsurge of mucormycosis during the second wave of the COVID-19 pandemic in India has become a burning issue and focus of interest. Authors here have shared their experiences of dealing with mucormycosis cases within the limited scope of this study.

Facial or periorbital pain and edema were the most common presentation in our study. This finding was in concurrence with Sen *et al*.[6] As fungus invades the orbit mostly from the paranasal sinuses, it commonly involves the medial and inferior orbit first. The medial orbit was predominantly affected in 27% of the cases. This could be through the nasolacrimal duct or the lamina papyracea. The orbital apex was involved in 5 (11.6%) of the patients. As already mentioned, optic nerve involvement – as evidenced clinically and radiologically – was the predominant cause of visual deprivation in this series. The optic nerve was compressed mostly at the apex, causing orbital apex syndrome or by diffuse orbital involvement. In a retrospective analysis of orbital mucormycosis in the pre–COVID–19 era, Jiang *et al*. reported orbital apex syndrome an initial presentation.[7]

Anatomically, ophthalmoplegia caused by III, IV, and VI nerve compression – in isolation or combined – may be due to compression at the superior orbital fissure by the disease process itself or due to CNS involvement, leading to compression of nerves at the cavernous sinus. Facial nerve palsy leading to lagophthalmos can also be a presenting symptom. Several hypotheses have been proposed, notably by Mehta *et al*., regarding facial nerve involvement.[8] The facial nerve can be involved either due to bony erosion from the maxillary sinus to premaxillary space and cheek or through the pterygopalatine fossa to infratemporal fossa. The trigeminal nerve may also be involved in the cavernous sinus. In our study, 26 (60.46%) patients presented with ophthalmoplegia and 2 (4.6%) patients presented with both trigeminal and facial palsy.

Panophthalmitis in mucormycosis is rare. Very few cases have been reported to date where panophthalmitis has occurred due to mucormycosis.[9] However, one of our study participants developed panophthalmitis and subsequently had to undergo exenteration.

The combined treatment with intravenous amphotericin and surgical debridement showed 70% survival. Much lower rates of survival had been observed with either medical or surgical treatment alone.[10] As already mentioned, we have followed the management guideline for COVID-19-associated orbital mucormycosis as suggested by Honavar[5] All patients in our series received intravenous liposomal amphotericin B (5–10 mg/kg) for about 30 days, followed by step-down therapy with oral posaconazole 300 mg BD on day 1, followed by 300 mg OD for the next 3 months. The main surgical procedure practiced was the debridement of paranasal sinuses and removal of necrotic tissue with irrigation of amphotericin B.

Several case reports have suggested the role of intraorbital injection of amphotericin B deoxycholate at a dose of 3.5 mg/mL to limit the local spread of the disease in orbit and for eye salvage.[11] Although there is a paucity of data, in our study, retrobulbar amphotericin B at a dose of 3.5 mg/mL was given in 22 patients, with a mean number of injections 1.9 (±0.52) per patient as an adjunct to medical and surgical therapy. This locally applied amphotericin B injection might have restrained the disease process in and around the orbit.

It needs to be emphasized that the removal of an eye causes a significant psychosocial impact. The decision to exenterate should, therefore, be well balanced between preserving the eye and preventing further intracranial spread and eventual death. Needless to say, where preservation of life becomes an issue, vision becomes a minor concern. The largest reported study of 2826 mucormycosis patients from India recommended exenteration from Stage 3C onward,[6] whereas a more conservative approach was suggested in Stage 3B or better. The study also emphasized that exenteration might be beneficial in preventing CNS spread. We followed this recommendation and 9 (20.9%) patients had to undergo exenteration in our study.

A similar uptick in mucormycosis cases had also been noted during the SARS-CoV outbreak in 2003. Fungal infections showed a rise of about 14.8%–27%.[12] COVID-19 is biologically similar to SARS-CoV,[13] it appeared that history has repeated itself. At present, an incidence of 26.7% for invasive fungal infections has been reported by White *et al*.,[14] which is quite similar to the situation during the 2003 episode.

Many hypotheses have been put forward for the resurgence of mucormycosis during this COVID-19 pandemic. COVID-19 itself is known to produce a hypoxic environment.[15] Furthermore, this virus has a reported activity against the pancreatic islet cells, causing high blood glucose levels. In acute-phase reactant,

serum ferritin level also rises. The phagocytic activity of leukocytes gets attenuated due to immunosuppression by the virus itself and the corticosteroids and immunosuppressants used in its management. Mucor is a commensal of the healthy nasal mucosa; this environment favors fungal spores to germinate, proliferate within the paranasal sinuses and spread to nearby structures, including the orbit.[15] Nosocomial infection, breach in hospital infection control measures, and the use of immunosuppressants are other risk factors attributed to the increased incidence of COVID-19-associated orbital mucormycosis.[15]

The role of corticosteroids in the resurgence of mucormycosis has also been well emphasized in various publications. The RECOVERY trial has established the benefits of corticosteroids in reducing mortality in patients with moderate-to-severe COVID-19.[16] Worldwide, it has been reported that 76% of the patients with COVID-19-associated orbital mucormycosis have a history of therapy with systemic corticosteroids.[15] Data from India reported around 88% of patients[17] requiring the same. In our study, all COVID-positive patients (37.86%) had a history of steroid exposure. Our data revealed that intravenous corticosteroids had been used in 78.37% of patients. Although the duration of steroid exposure was within the stipulated recommendation,[18] usage of the same could be a possible cause for orbital mucormycosis.

There has been a wide variation in the durational gap between the detection of COVID-19 positivity and the diagnosis of mucormycosis. In our study, mucormycosis had been detected after an average of 25.08 ± 18.70 days from the detection of COVID-19. As per available literature, the shortest duration has been reported to be 10 days with the longest average duration being 2-month post-COVID-19 positivity.[19,20] In our study, 37 (90%) patients were RT-PCR positive for COVID-19 and rest 6 (10%) patients were RT-PCR negative for COVID-19. This can be due to two factors. First, these patients recovered from COVID-19 and became seronegative. The second possibility is *de novo* ROCM happening during the COVID-19 pandemic. Patients with comorbidities and any form of immunosuppression have a greater chance to develop this opportunistic fungal infection. Among all comorbidities, diabetic people are at a seven times higher risk to develop mucormycosis.[21]

The COVID-19 virus damages pancreatic islet cells. This causes new-onset diabetes or worsens preexisting diabetes.[22] The ensuing cytokine storm also worsens the hyperglycemic condition by producing insulin resistance.[17] Furthermore, the glycosylation of transferrin and ferritin causes reduced iron binding. Thus, acidosis presents an additive effect, causing an overall increase in free iron levels.[22] Mucor depends on this free iron and utilizes the same to germinate well. When we look at the current scenario of COVID-19-associated orbital mucormycosis in India, 93% of patients were diabetics.[17] Existing global data also show that diabetics account for 80% of the cases. Concomitant DKA was found in 15%–41% of these patients and 80.3% of them were uncontrolled.[15,19] In this study, 95% of participants had diabetes, 15 (34.88%) were uncontrolled, and 3 (6.97%) had ketoacidosis on presentation.

Chronic kidney disease (CKD) is another important comorbidity associated with COVID-19-related mucormycosis. It has been reported that the proportion of CKD among COVID-19 patients (4.09%) is higher than the general population (0.46%). CKD has been identified as a mortality predictor of COVID-19-related mucormycosis.[23,24] In our study, 2 (4.6%) patients had CKD, required hemodialysis but unfortunately expired.

The etiology of resurgence during the present phase could therefore be attributed to the significant surge in cases of uncontrolled diabetes along with poor medical control. Lack of adequate medical care and an overburdened health system are other contributory factors. Surge of aggressive fungal infections, especially mucormycosis, have been reported after other natural disasters as well.[25,26] There is scope for further studies to find out the reasons for the unprecedented rise of orbital mucormycosis.

Literature reports orbital mucormycosis associated with COVID-19 has an overall mortality of around 31%.[15] Results from our series showed that overall mortality with COVID-19 associated was 30.23%. Mortality audit showed all 13 (30.2%) patients who died in our series had diabetes, including two who had diabetic ketoacidosis. The recovery status of this series revealed that the disease regressed in 20 (46.5%) patients. The visual outcome of the study participants showed that 20 (46.5%) patients maintained visual acuity of 6/9 and better.

The prognostication of COVID-19-associated mucormycosis could be determined on several risk factors. Our data showed the presence of a more advanced stage of disease (Stage 3C or worse), uncontrolled diabetes, and CKD carried a higher risk of mortality. This understanding is in accordance with articles published by Ravani[20] and Sen *et al*.[6]

The study was, however, not without its limitations. A long-term study which shall include the outcome of surgical and medical management is needed. The psychosocial impact of exenterated patients also needs to be evaluated. Furthermore, information about vaccination status, RT-PCR status, including cycle

threshold value, and its relation to mucormycosis, if any, also needs to be studied.

Conclusion

The authors conclude that a hyperglycemic state – due to diabetes, COVID-19-associated islet cell damage or systemic steroid usage – was one of the most important predisposers to mucormycosis infection. Concomitant immunosuppression worsened the situation. Orbital and ophthalmic involvement was fairly common, and preservation of visual function was a major challenge. A combination of medical and surgical approaches along with intraorbital antifungal injection appeared to be beneficial. However, a more detailed study with a larger sample size and a longer follow-up period would certainly be academically more rewarding.

Data availability statement

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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Nil.

Conflicts of interest

The authors declare that there are no conflicts of interest in this paper.

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