

A study on clinico-radiological profile, risk factors, and management of mucormycosis during COVID pandemic in Rewa, (M.P.)



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ABSTRACT

Background: Second wave of coronavirus disease 2019 (Covid-19) pandemic has been particularly devastating in India. COVID-19 and mucormycosis (also known as black fungus) are causing comorbid conditions to worsen the extent of infection and mortality rates especially in India. Mucormycosis can involve nose, sinuses, orbit, central nervous system, lung (pulmonary), gastrointestinal tract any many other organs, but rhino orbital cerebral mucormycosis is the most common variety seen. Rapidity of dissemination of mucormycosis is an extraordinary phenomenon and a delay in the diagnosis could be fatal. **Aims and Objectives:** The objective of this study is to document the clinical features, radiological extent, risk factors, management, and outcome of mucormycosis. **Materials and Methods:** The study was retrospective observational study. Eighty-two mucormycosis patients admitted in SGMH Rewa were selected as study subjects. Data regarding clinical features, radiological extent, associated risk factors, comorbidities, management during hospital stay, and outcome of mucormycosis patients were collected on excel sheet and analyzed using appropriate statistical tests. **Results:** In our study, majority of the patients were unvaccinated (88%). Most common presenting complaint was nasal congestion with or without discharge in 78% patients followed by Facial swelling, visual disturbances, facial weakness, dental pain, etc. On CT or magnetic resonance imaging examination, all cases of mucormycosis had maxillary sinus (100%) involvement, followed by ethmoid (82%) and sphenoid (78%) sinuses. Diabetes mellitus was most common comorbidity seen in 52% cases. About 83% cases had history of receiving high dose steroid intravenously during management of COVID illness. Among study cases 72% patients have taken oxygen supplementation for more than 72 h, for COVID-19 pneumonia before hospitalization for mucormycosis. Therapy of Liposomal Amphotericin B and Oral Triazole (predominantly oral Posaconazole) was the most common medical treatment offered to all patients with COVID associated mucorpatient. Functional endoscopic sinus surgery was done on 93% cases followed by Modified Denker's procedure was done in 12% cases. **Conclusion:** In our study, mucormycosis appears to be associated with COVID-19, diabetes, and use of corticosteroids. Full vaccination with COVID-19 vaccines, judicious use of corticosteroids in patients with COVID-19 and strict control of blood glucose level along with timely and proper management is highly recommended to reduce the incidence of fatal mucormycosis.

Key words: Mucormycosis; Diabetes mellitus; Corticosteroids; Covid-19

INTRODUCTION

Coronavirus disease 2019 (COVID-19) pandemic left the world reeling over the past year. The second wave has been

particularly devastating in India. During April and early May 2021, millions were affected and thousands were seeking hospital care. Secondary infections are known to complicate the clinical course of COVID-19. COVID-19-associated

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mucormycosis can be a serious complication of COVID-19 which may worsen the extent of infection and mortality rates. Mucormycosis (also known as black fungus) is an opportunistic infection leading to invasion of blood vessels by fungal hyphae, causing infarction and necrosis of a variety of end-organ host tissues.¹ Mucormycosis can involve nose, sinuses, orbit, central nervous system (CNS), lung (pulmonary), gastrointestinal tract, skin, jaw bones, joints, heart, kidney, and mediastinum (invasive type), but rhino orbital cerebral mucormycosis (ROCM) is the most common variety seen.² *Rhizopus Oryzae* is most common type and responsible for nearly 60% of mucormycosis cases and also accounts for 90% of the rhino-orbital-cerebral (ROCM) form.³

India has highest cases of the mucormycosis in the world. ROCM type is the most common form of mucormycosis in India, followed by the pulmonary and cutaneous types.⁴ ROCM refers to the entire spectrum ranging from limited sino-nasal disease (sino-nasal tissue invasion), limited rhino-orbital disease (progression to orbits) to rhino-orbital-cerebral disease (CNS involvement).⁵ Moreover, rapidity of dissemination of mucormycosis is an extraordinary phenomenon and a delay in the diagnosis could be fatal.

Aims and objectives

We have conducted a retrospective observational study in our institute with an objective to document the clinical features, radiological extent, risk factors, management, and outcome of mucormycosis which poses a potential threat to Covid-19 pandemic.

MATERIALS AND METHODS

The present observational study was conducted among mucormycosis patients who fulfilled the inclusion criteria.

Study design

This was a retrospective observational study.

Study sample

Eighty-two cases of mucormycosis admitted in Sanjay Gandhi Memorial Hospital Rewa from May to August 2021 constituted our study sample.

Inclusion criteria

Subjects included in this study were clinically and microbiologically proven cases of mucormycosis with concurrent or prior history of COVID-19. In clinically suspected patients, presence of fungal hyphae, characteristic of Mucorales fungi, by direct examination in 10% potassium hydroxide (KOH) from scrapping and biopsy was used for diagnosis.

Exclusion criteria

Patients of mucormycosis with no prior or active COVID-19 infection were excluded from the study.

Data collection methods

The study was approved by our institutional ethics committees. Data were obtained from health record of each patient. Data pertaining to demographics, clinical features, co-morbidities, COVID-19 related hospitalization, treatment received including steroids, use of supplemental oxygen, mechanical ventilation, medical and surgical management, and hospitalization outcomes were obtained after obtaining informed consent from patients. Computed tomography (CT) and/or magnetic resonance imaging (MRI) of the orbit, brain and/or paranasal sinuses were performed for all cases to assess the extent of involvement from mucormycosis.

Statistical analysis

Data were compiled and entered in Microsoft Excel, analyzed and interpreted using descriptive statistics, statistical analysis was performed using SPSS Version 20. Chi-square test was applied to find association and $P < 0.05$ was considered statistically significant.

RESULTS

Majority patients were males (77%) and 23% were females. (Table 1) Mean age was 52.8 years. Only 12% patients were vaccinated and 88% were unvaccinated. 93% patients were post-COVID patients and 7% patients had active COVID infection at the time of admission. (Table 2) Most common presenting complaint was nasal congestion with or without discharge in 78% patients followed by Facial swelling (48%), diplopia (43%), facial numbness (40%), headache (38%), visual disturbances (35%), facial weakness (28%), dental pain (22%), etc. (Figure 1) Black discoloration of skin and mucosa along with ulceration and discharge from

Table 1: Gender-wise distribution of cases of mucormycosis

Gender	No.	%
Male gender (%)	63	77
Female gender (%)	19	23
Total	82	100

Table 2: Status of COVID-19 and vaccination at time of presentation

COVID-19 vaccination status	No.	%
Unvaccinated	72	88
1 dose vaccinated	9	11
2 doses vaccinated	1	1
COVID status		
Active COVID cases	6	7
Post-COVID (history of COVID infection in past)	76	93

nose, palatal mucosa was characteristic of mucor infection. CT scan demonstrates bone dehiscence or destruction hence considered the first modality for imaging. MRI is useful in demonstrating the optic nerve, intracranial and vascular invasion. On CT or MRI examination, all cases of mucormycosis had maxillary sinus (100%) involvement, followed by ethmoid (82%) and sphenoid (78%) sinuses. Pansinusitis was noted in 73% cases of mucormycosis. About 40% cases showed rhino-orbital invasion and 26% showed intracranial invasion, that is, ROCM. (Table 3)

Among comorbidities, diabetes mellitus was most common comorbidity seen in 52% cases followed by hypertension in 17% cases. (Table 4) Among study cases, 38% patients had history of admission in hospital for management of COVID-19 infection more than a week, and 34% cases had history of admission in hospital for

3–7 days for management of COVID-19 infection before hospitalization for mucormycosis. About 72% patients had taken oxygen supplementation for more than 72 h for COVID-19 pneumonia before hospitalization for mucormycosis and 40% had history of use of mechanical ventilator support for management of COVID-19 infection before hospitalization for mucormycosis. About 83% cases had history of receiving high dose steroid intravenously during management of COVID illness, and of them 10% received intravenous steroid for <72 h, 34% received IV steroid for 72 h–7 days while 39% mucormycosis cases took IV steroid for more than 7 days. (Table 5)

Therapy of liposomal Amphotericin B and oral triazole (predominantly oral posaconazole) was the most common medical treatment offered to all patients with Covid associated mucorpatient (CAM). In our study also, most commonly used antifungal drug was liposomal Amphotericin B in 73% cases followed by Posaconazole used in 15% cases and Isavuconazole in 9% cases.

Surgery at an early stage is better than late because drugs do not reach the necrotic tissue. Most common surgical procedure performed was functional endoscopic paranasal sinus surgery (FESS) with debridement of necrosed and diseased sinus tissue in 93% mucormycosis cases followed by Modified Denker’s procedure was done in 12% cases. Modified Denker’s procedure was done in Functional endoscopic Debridement (FESS) failure cases. (Table 6)

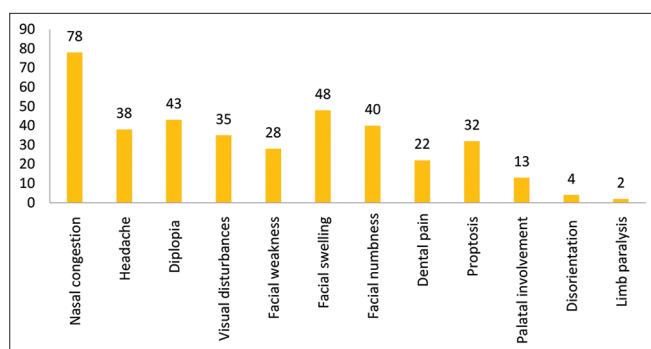


Figure 1: Presenting complaints at the time of admission

Table 3: Radiological characteristics of mucormycosis cases		
Radiological characteristic	No.	%
Sinus involvement based on CT PNS or MRI findings		
Pan-sinusitis	60	73
Frontal	61	74
Maxillary	82	100
Ethmoid	69	82
Sphenoid	64	78
Mucormycosis with extension beyond paranasal sinuses	62	76
Orbital invasion	33	40
Intracranial invasion	21	26

Table 4: Co-morbidities associated with mucormycosis		
Co-morbidities	No.	%
Diabetes mellitus	43	52
Hypertension	14	17
Ischemic heart disease	4	5
COPD	2	2
Rheumatoid arthritis	1	1
Hypothyroidism	4	5
Sinusitis	5	6

Table 5: Management in hospital before diagnosis of mucormycosis cases		
Length of hospital stay during COVID management before diagnosis of mucormycosis		
	No.	%
No admission required	17	20
Less than 72 h	06	7
>72 h–<7 days	28	34
>7 days	31	38
Duration of high flow oxygen therapy during COVID management before diagnosis of mucormycosis		
	No.	%
Not required	19	23
<72 h	4	5
>72 h	59	72
Duration of mechanical ventilation during COVID management before diagnosis of mucormycosis		
	No.	%
Not required	49	60
Less than 72 h	1	1
>72 h	32	39
Duration of use of IV steroid		
	No.	%
Not required	14	17
Less than 72 h	9	10
>72 h–<7 days	28	34
>7 days	31	39

As the disease is known to be aggressive, mortality is more than 50%. The mortality increases to 80% with an intracranial extension of the disease.⁶ Out of 82 cases, 26 cases died and 56 cases survived. (Figure 2) Association between duration of high flow oxygen use during COVID management and survival rate was found to be statistically highly significant. (Chi-square statistic – 22.21, P<0.001). Association between duration of steroid use during COVID management and survival rate was found to be statistically highly significant (Chi-square statistic- 12.06, P<0.001).

DISCUSSION

Mucormycosis or zygomycosis, also called phycomycosis, is an uncommon and aggressive fungal infection that usually affects patients with alteration of their immunological system. COVID-19 patients always have immunosuppression with a decrease in CD4+ T and CD8+ T cells along with diffuse alveolar damage with severe inflammatory exudation predisposing the risk of mucormycosis.⁷

In our study, 93% cases had prior history of COVID infection and they had recovered from their COVID illness

Table 6: Treatment of mucormycosis		
Anti-fungal treatment		
	No.	%
Liposomal Amphotericin B	60	73
Conventional Amphotericin B	3	4
Posaconazole	12	15
Isavuconazole	7	9
Type of surgery for the treatment of mucormycosis		
	No.	%
Could not performed	6	7
Modified Denker's procedure	10	12
Functional endoscopic paranasal sinus surgery (FESS)	76	93

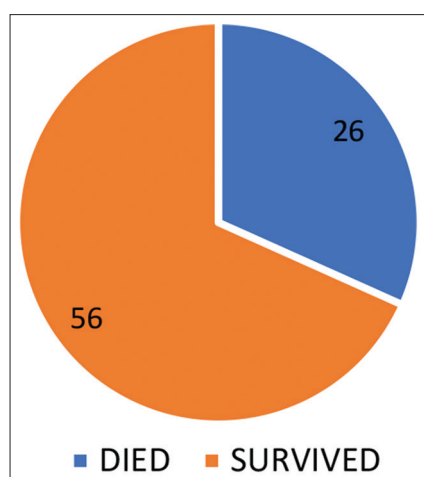


Figure 2: Outcome of mucormycosis cases

(post-COVID) and 7% cases had active COVID infection. Similar findings were reported by Sharma et al., that out of 23 CAM 17% patients were coronavirus-positive and had been infected for more than 14 days; remaining 83% had been infected earlier and had recovered (post Covid).⁸

COVID vaccination status have played very crucial role in our study, as 88% CAM cases were unvaccinated. Unvaccinated patient had severe COVID infection that requires long hospital stay, longer exposure of steroid, and longer oxygen supplementation and ventilator support.

Diabetes mellitus has been the most common risk factor linked with mucormycosis. Uncontrolled hyperglycemia in diabetic cases can alter immunologic response, leading to increased extent of fungal infection. The mucormycosis stemming from COVID-19 patients has been more commonly observed in patients with a history of diabetes mellitus and 95% of individuals with severe or critical COVID-19.⁹ Innate immunity and adaptive immunity comprise the immune system of the human body. Neutrophils, natural killer (NK) cells, and dendritic cells play a crucial role in innate immunity, whereas B lymphocytes and T lymphocytes are part of adaptive immunity. DM impairs the ability of the human body to fight infection by interfering with innate and adaptive immunity. Dendritic cells are antigen-presenting cells that present antigen to immune cells and help them in the recognition and neutralization of infecting agents. Hyperglycemic patients are more susceptible to infection because of the reduced number of dendritic cells in circulation, increased apoptosis of NK cells, and neutrophilic dysfunction.¹⁰

In our study, 52% CAM cases had uncontrolled DM at the time of admission. Concordant findings were also observed in other studies. Swati et al. concluded that major risk factors for mucormycosis in the times of COVID-19 included uncontrolled diabetes (96.7%).¹¹ According to Singh et al., 92% patients of mucormycosis had DM.¹² Prakash et al. also found that 18% had DKA and 57% of patients had un-controlled DM.¹³ The presence of DM increases the odds of contracting ROCM by 7.5-fold was shown in a prospective Indian study, before COVID-19 pandemic.¹⁴ In a recent systematic review conducted until April 9, 2021 by John et al., DM was reported in 93% of cases, while 88% were receiving corticosteroids.¹⁵ A study done by Patel et al. found that 65% of CAM patients had uncontrolled diabetes.¹⁶

Corticosteroids have a strong anti-inflammatory effect and play role in treating immunologic complications of COVID-19 infection such as cytokine storm and lung inflammation. Furthermore, corticosteroids have been associated with an increased risk of superinfection

including bacterial, mycobacterial, and fungal infections.¹⁷ A complex coordination of factors lead to systemic immune alterations and hampers innate immunity by reducing T lymphocytes, CD4+ and CD8+ cells in the body in COVID-19 patients, that gives rise to secondary infections.¹⁸ In our study, 83% cases had history of receiving high dose steroid intravenously during management of COVID illness, and of them 10% received intravenous steroid for less than 72 h, 34% received IV steroid for 72 h–7 days while 39% mucormycosis cases took IV steroid for more than 7 days. Similar findings were observed in other studies. Bhanuprasada et al. have shown in his study that steroid use was significantly associated with mucormycosis (OR 28.4; P=0.001).¹⁹ Ramaswami et al. have also shown in his study that total 70% had received steroids for COVID-19 disease prior to CAM symptoms. About 15.7% received both inhalational and systemic steroids. Systemic steroids were prescribed for a median duration of 7.5 days (IQR: 7–10.5).²⁰ About 46% patients received corticosteroids within the month before the diagnosis of mucormycosis in the European Confederation of Medical Mycology study.²¹ In our study, 77% cases required high flow oxygen supplement, of which 72% CAM cases required oxygen supplementation for more than 72 h for COVID-19 infection management while a study of Mitra et al. showed that 28.1% patients received high flow nasal oxygen in a hospital setup for management of COVID-19 illness.²² Our study results find that prior COVID infection disturb the immune system and make body a fertile soil for mucor infection. Diabetes mellitus as co morbidity and exposure of steroid, long term oxygen therapy with long hospital stay, flair up the mucor infection. More the severity of Covid required longer hospital stay, longer steroid exposure, and oxygen inhalation and ventilatory support need that make the patient more prone for mucor infection. Therapy of liposomal Amphotericin B (73%) and oral triazole predominantly oral posaconazole (15%) was the most common medical treatment offered to all patients with CAM as seen in our study also. Surgery at an early stage is better than late, because drugs do not reach the necrotic tissue. Most common surgical procedure performed was functional endoscopic paranasal sinus surgery (FESS) with debridement of necrosed and diseased sinus tissue in 93% mucormycosis cases followed by Modified Denker's procedure was done in 12% cases. Similarly in a systemic review done by Jafar A majority of the patients in their review underwent surgical resection/debridement.²³ As the disease is known to be aggressive, with high mortality and that increases further with an intracranial extension of the disease. In our study, out of 82 cases, 26 cases died and 56 cases survived. Highly significant association of disease outcome with oxygen and steroid use during COVID management was seen in our study.

Limitations of the study

The limitation of our study is that Covid Severity Score by radiological imaging could not be assessed.

CONCLUSION

In our study, COVID-19 vaccination plays a major role in reducing the occurrence of mucormycosis in COVID infection. Along with the altered immune status in Covid-19 infection, diabetes mellitus specially uncontrolled, use of steroid for longer duration, longer hospitalization and oxygen inhalation therapy for COVID management were very important risk factors for ROCM. We recommend full COVID-19 vaccination, management of co morbidities specially strict control of blood sugar in diabetic patients, rational use of steroid during Covid-19 management to reduce severity of COVID infection and hospitalization, and that reduces the burden of super infection of mucormycosis in COVID cases. Mortality associated with mucormycosis in India is considerably high due to delay in diagnosing the disease, seeking medical attention and challenges faced in managing advanced stage of infection. Early diagnosis in suspected cases with prompt management by susceptible antifungal drugs, with necessary surgical intervention, and proper comorbidity management could be of great help in improving prognosis of patients.

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PI - Concept of study and prepared first draft of manuscript. **AA** - Coordination and preparation and revision of the manuscript. **YS** - Literature Review, data collection, and manuscript preparation. **SN** - Design of study, statistical analysis, and manuscript preparation. **MI** - Preparation and revision of the manuscript.

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