

ORIGINAL RESEARCH

Analysis of Risk factors in Post-COVID-19 Rhino-Orbital-Cerebral Mucormycosis and Survival outcome in high risk or immune-compromised Patients

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ABSTRACT

Objective: This study was undertaken to identify possible risks and associations of COVID-19 infection and immune-compromised state with increased incidence of mucormycosis and the survival outcome in patients with Rhino-Orbital-Cerebral Mucormycosis (ROCM). **Background:** The 21st century witnessed a significant downturn in global population health due to the COVID-19 pandemic. While medical professionals were still grappling with the treatment of coronavirus, a more deadly infection, Mucormycosis emerged as an epidemic, posing the greatest challenge yet. **Methods:** In this retrospective study, all the cases diagnosed with mucormycosis from March 2021 to November 2021 were taken into the study. This time period contributes to the second wave of COVID-19 when Mucormycosis was declared 'epidemic in the pandemic'. A total of twenty-one patients were diagnosed with Mucormycosis in the period of nine months. **Results:** Out of twenty-one enrolled patients' details, all had a recent (about 1 month) history of moderate to severely symptomatic COVID-19 infection and thus received either of oral or parenteral corticosteroid treatment. The incidence of diabetes mellitus was 57.14% among subjects, and 28.57% were into ketoacidosis at the time of diagnosis for mucormycosis. All the patients received Amphotericin-B 50mg/kg ranging from 7 to 14 days, subject to availability followed by Posaconazole and voriconazole treatment. 71.43% of cases recovered while 28.57% died from brain involvement of fungus i.e., Rhino-Orbital-Cerebral Mucormycosis (ROCM). **Conclusion:** An immunosuppressive environment created due to COVID-19, diabetes mellitus, and extensive use of corticosteroids provides a suitable medium for fungus to grow and thus increases the incidence of mucormycosis.

Key words: COVID-19, Mucormycosis, Opportunistic Infections

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INTRODUCTION

The 21st century witnessed a significant downturn in global population health due to the COVID-19 pandemic. While medical professionals were still grappling with the treatment of coronavirus, a more deadly infection, Mucormycosis emerged as an epidemic, posing the greatest challenge yet. Mucorales fungi, particularly *Rhizopus-oryzae*, exhibit rapid filamentous growth in favorable conditions and are capable of angioinvasion, resulting in thrombosis and tissue necrosis.¹ These fungi have a high mortality rate, exceeding 50%, due to their

aggressive invasive nature, resistance to treatment, and delayed management.²⁻⁴ It is frequently seen as an infection that takes advantage of a weakened immune system, but it can also occur in the absence of any underlying condition.¹ The vulnerability to it primarily affects those with weakened immune systems resulting from conditions such as diabetes, long-term corticosteroid use or high-dose therapy, organ transplant recipients, HIV-positive individuals, neutropenia, malnutrition, hemochromatosis, hematologic malignancies, and other immunosuppressed conditions.^{2,3} The incidence of

mucormycosis has been suggested to increase contrary to the widespread administration of systemic corticosteroids, tocilizumab, mechanical ventilation, and supplemental oxygen in clinical settings associated with COVID-19, diabetes mellitus, and other immunocompromised diseases.²

METHODS

Study Design: Present study was a retrospective study conducted on admitted patients (in-patients) at our institute.

Patients: All the patients diagnosed with mucormycosis from March 2021 to November 2021 were taken into the study. The consent from the study cases has not been taken due to retrospective analysis of medical records but anonymity has been maintained in this analysis. The approval from Institutional Ethical Committee has been obtained to undertake this analysis.

Diagnostic criteria: Patients with clinical features and mycological/histopathological evidence of mucormycosis in tissue biopsy (including observation of aseptate hyphae associated with tissue damage) taken by functional endoscopic sinus surgery (FESS) or needle aspiration. All the demographic and clinical characteristics comprising ophthalmic and neurological manifestations, underlying conditions, as well as medical and surgical interventions were recorded. CT scans of paranasal sinuses, such as evidence of mucosal thickening, turbidity, and bone destruction were done.

RESULTS

Over a period of nine months, 21 cases of mucormycosis have been diagnosed in the hospital, and their demographic data is provided in Table 1.

Table 1: The demographic profile of the study patients.

Parameter		Total patients (n)= 21	Percentage
Gender	Male	14	66.7 %
	Female	7	33.34 %
	M:F ratio	2:1	
Age	Range	23-81 years	
	Mean Age	55±16 years	

In our study, 17 out of 21 patients were co-morbid with existent diabetes and hypertension. Six (28.57%) were undergoing diabetic ketoacidosis management when the first symptom of mucormycosis occurred. The profile of co-morbidities of the patients is provided in Table 2.

Table 2: The co-morbidity profile of the study patients.

Co-morbidities		Total patients (n)= 21	Percentage
1. Diabetics	Total	12	57.1 %
	Male	8	38.1 %
	Female	4	19.1 %
2. Hypertensive	Total	5	23.8 %
	Male	3	14.3 %
	Female	2	9.5 %
3. Both DM + HTN	Total	4	

The extent of spread of fungus in patients was done on the basis of clinical features and mycological/histopathological evidence of mucormycosis in tissue biopsy (including observation of aseptate hyphae associated with tissue damage) taken by functional endoscopic sinus surgery (FESS) or needle aspiration. Direct examination of the biopsy or aspirated material was performed using 10% potassium hydroxide (KOH). The growth of pure and similar colonies of Mucorales on more than one culture media was considered significant. The extent of involvement by fungus in study patients is provided in Table 3.

Table 3: The extent of involvement of the fungus (mucormycosis) in the study subjects.

Mucormycosis extent of involvement	No. of cases	Percentage
Upto Nasal mucosa only (Nasal)	4	19%
Upto Nasal mucosa with Paranasal sinus (Sino-nasal)	6	28.6 %
Upto Nasal mucosa with orbit (Sino-naso-orbital)	5	23.8 %
Upto Nasal mucosa with brain involvement (Rhino-orbito-cerebral Mucormycosis)	6	28.6 %

Functional Endoscopic Sinus Surgery (FESS) has been performed in more than half of the patients who underwent early diagnosis. Conventional

Amphotericin-B treatment (average total dose of 50mg/day) was administered for 3-11 days, subjected to availability, when the availability of Amphotericin-

B was also a hurdle to overcome with. Furthermore, patients received Posaconazole and Voriconazole for 14-21 days on the basis of their response to the treatment. In one patient, exenteration was performed after informed and signed consent to prevent the cerebral involvement of fungus. Fifteen (71.4%) patients recovered and were discharged with follow-up advice while the lethal outcome was observed in six patients (28.6%) due to cerebral involvement of the fungus.

DISCUSSION

In our study, all the cases had a history of recent COVID-19 infection and few were undergoing treatment for the same during the evidence of the first symptom. The range of time interval between Covid-19 infection confirmation and evidence of first mucormycosis symptom was 3rd to 45th day in patients with a mean/median of 17.3 days/11 days. Recent studies also stressed the fact that COVID-19 infection leads to an incompetent innate immune system.^{5,6} The diagnosed cases received Amphotericin-B treatment. Mohammadi R et al. also conducted a study on 22 patients that received the same treatment.⁷

According to our research, 57.1% of the patients already had Diabetes mellitus, proving that it is the most closely linked comorbidity with mucormycosis. Additionally, developing countries appear to have a higher susceptibility to developing Diabetes mellitus, which has been exacerbated by the rapid socioeconomic development and explosive increase in the number of Diabetes cases. A similar study done by Javadi et. al. reported nine mucormycosis cases among diabetic patients in Tehran and the mortality rate was 75% in their study.⁸ This also confirms the increased incidence of mucormycosis with pre-existing co-morbidities in the population.

Radiological scans commonly classify Rhino orbital involvement as the most frequent variant in mucormycosis, suggesting early involvement of the orbit. Unfortunately, this infection can rapidly spread to the brain, resulting in Rhino-orbital-cerebral-mucormycosis, which has an alarmingly high mortality rate of around 50%.⁹ In our study, mortality was observed in six patients (28.6%) due to cerebral involvement of the fungus.

CONCLUSION

To conclude, Covid-19 infection which itself produces an immunocompromised state and associated risk

factors like diabetes, hypertension, and abrupt use of corticosteroids and oxygen therapy increased the incidence of Mucormycosis, leading to high mortality rates. Aside from the effort to control known risk factors, physician awareness and a multi-disciplinary approach should be reinforced to enable earlier diagnostics and access to treatment.

DECLARATIONS

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Conflict of interest: None declared

Ethical approval: The study was approved by Institutional Ethical Committee, Pacific Medical College & Hospital (Ref no.- PMU/PMCH/IEC/2022/182E)

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