



Analysis Of Risk Factors In Post-COVID-19 Rhino-Orbital-Cerebral Mucormycosis And Survival Outcome In High Risk Or Immune-Compromised Patients

¹Sagar Dhillon, ²Sneha Dhillon, ³Rajendra Choudhary, ⁴Shruti Sharma

^{1,4}PG Resident, ²Assistant Professor, ³Associate Professor

^{1,3}Department of Ophthalmology, Pacific Medical College and Hospital, Udaipur, Rajasthan

²Department of Radiation Oncology, GCRI- Bhavnagar Cancer Care and Research Institute, Bhavnagar, Gujarat

⁴Department of General Surgery, Pacific Medical College and Hospital, Udaipur, Rajasthan

***Corresponding Author:**

Shruti Sharma

PG Resident, Department of General Surgery, Pacific Medical College and Hospital, Udaipur

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Abstract

Purpose

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.

Materials And Methods

In this retrospective study, all the cases diagnosed with mucormycosis and admitted for management at our institute 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.

Keywords: COVID-19, Mucormycosis, Opportunistic Infections

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 favourable 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

Materials And Methods

Study Design

Present study is a retrospective study conducted on admitted patients in Isolation wards (in-patients) at our institute.

Patients

All the patients diagnosed with mucormycosis from March 2021 to November 2021 were taken into the study. A total of twenty-one patients were diagnosed with Mucormycosis in the period of nine months. This time period contributes to the second wave of COVID-19 when Mucormycosis was declared 'epidemic in the pandemic'. The consent has not been taken from the study cases 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.

Data Analysis

The collected data were entered on a Microsoft excel sheet and then analyzed on Statistical Package for Social Sciences (SPSS) version 22.0. Mean±Standard Deviation (SD) was calculated for quantitative data. Percentage and proportion were calculated for qualitative data.

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.

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.

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.

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 from 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.

Tables

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	

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	

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 %

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.

References

1. Ghuman, Harlene, and Kerstin Voelz. Innate and adaptive immunity to mucorales. *J Fungus*. 2017;3(3):48.
2. AL-Khikani, Falah Hasan Obayes. Dermatophytosis a worldwide contiguous fungal infection: Growing challenge and few solutions. *Biomed. Biotechnol. Res. J* 2020;4:117.
3. AL-Khikani, Falah HO, and Aalae S. Ayit. Major challenges in dermatophytosis treatment: current

- options and future visions. *Egypt. j. Dermatol. venerol* 2021;41(1):1.
4. Al-Khikani, Falah HO, Huda AS Almosawey, Younus J. Abdullah, Atyaf A. Al-Asadi, Raghadah M. Hameed, et al. Potential antiviral properties of antifungal drugs. *J. Egypt. Women's Dermatologic Soc.* 2020;17(3):185
 5. Schulte-Schrepping, Jonas, Nico Reusch, Daniela Paclik, Kevin Baßler, Stephan Schlickeiser, et al. Severe COVID-19 is marked by a dysregulated myeloid cell compartment. *Cell J.* 2020;182(6):1419-1440.
 6. Parackova, Zuzana, Irena Zentsova, Marketa Bloomfield, Petra Vrabcova, Jitka Smetanova, et al. Disharmonic inflammatory signatures in COVID-19: augmented neutrophils' but impaired monocytes' and dendritic cells' responsiveness. *Cell J.* 2020;9(10):2206
 7. Mohammadi R, Meidani M, Mostafavizadeh K, Iraj B, Hamedani P, Sayedain SM, et al. Case series of rhinocerebral mucormycosis occurring in diabetic patients. *Caspian J Intern Med.* 2015;6(4):243.
 8. Mohammadi SH, Daneshi A, Javadi M. Orbitorhinocerebral mucormycosis: report of 9 cases. *Razi Journal of Medical Sciences.* 2002;8(26):397-407.
 9. Weykamp, Cas. HbA1c: a review of analytical and clinical aspects. *Ann. Lab. Med.* 2013;33(6):393-400.