

Brief Report

Clinical characteristics and analysis of treatment outcome at one year of rhino-orbito-cerebral mucormycosis cases during the second wave of the Covid-19 pandemic (2nd wave); experiences from a tertiary care hospital in Kolkata, India.

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Abstract

Literature published between December 2019 and March 2021 suggested that India had contributed to approximately 71% of the total global cases of mucormycosis in patients with COVID-19. This study aimed to analyse the clinical patterns and evaluate treatment outcomes at twelve months of rhino-orbital-cerebral mucormycosis (ROCM) diagnosed during the Covid-19 pandemic second wave.

A prospective observational study was carried out at the School of Tropical Medicine, Kolkata between April 2021 and May 2021. Intravenous liposomal amphotericin B injection (10 mg/kg/day for 42 days in patients with cerebral involvement and 5mg/kg/day for 21 days in patients with non-cerebral involvement) was initiated followed by oral posaconazole (300 mg twice on the first day, followed by 300 mg daily for 6–12 months) (as per ICMR guidelines). Diabetes and other co-morbidities were adequately optimised.

Seventeen patients were admitted with symptoms of ROCM with males outnumbering females. Four patients (23.5%) with extensive cerebral involvement died within the first week of initiation of treatment. Three (17.6%) patients had diabetic ketoacidosis. The survival rate of overall ROCM was 76.5%.

The study shows that timely diagnosis and appropriate treatment reduces the mortality of ROCM except in cerebral involvement, where the outcome was guarded despite aggressive treatment. Six-month treatment was inadequate in most of the cases, and multiple surgical interventions along with antifungals accelerated the recovery.

Keywords: *Rhino orbital cerebral mucormycosis, Covid-19.*

Introduction

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Mucormycosis, though rare, is an aggressive opportunistic acute fungal infection caused by fungi belonging to the phylum Glomeromycota, subphylum mucormycotina. Globally, *Rhizopus*, *Lichtheimia*, *Mucor*, *Rhizomucor* are the common species with *Rhizopus arrhizus* responsible for most cases of mucormycosis in India, with species variations in different geographic regions.¹ Infection through inhalation of spores is common with other routes being percutaneous inoculation and ingestion. This angio-invasive fungus needs a favourable environment for the germination of spores. Poorly controlled diabetes mellitus, severe neutropaenia, haematological malignancies, patients having solid organ transplantation, on corticosteroids and/or immunosuppressants are the major risk factors precipitating the infection.² Prevalence of mucormycosis varies from 0.005 to 1.7 per million population globally while it is 80 times higher (0.14 cases per 1000 population) in India.³ During the second wave of the Covid-19 pandemic in early 2021, there was a marked increase in mucormycosis reported from different countries including India and fungal co-infection constituted 48% of Covid-19 studies.⁴ During the first wave of COVID-19, the Union Health Ministry did not release any official figures regarding mucormycosis.

The aims of the study was to analyse the clinical patterns and evaluate the outcome of treatment at 12 months in respect of ROCM diagnosed during the second wave of the Covid-19 pandemic. Carmichael Hospital of Tropical Diseases, Kolkata usually deals with all the tropical diseases in eastern India, where there was a sudden increase in post-covid mucormycosis cases during April-May 2021.

Methods

This observational study was done prospectively at Carmichael Hospital of Tropical Diseases, Kolkata. Patients with ROCM were enrolled for a period of two months during the second phase of Covid-19 (1st April-31st May). Only diagnosed cases of ROCM were enrolled during this period and were followed up for the next 12 months. Mucor-affected tissues were sent for microbiological examination including conventional microscopy, culture and histopathology.

Microscopy: Potassium hydroxide mounts with or without calcofluor stain was performed. The samples were incubated at 25 °C and 37 °C after inoculation on paired sets of Sabouraud Dextrose Agar. Positive cultures were identified through macroscopic and microscopic features. Haematoxylin-eosin, Periodic Acid-Schiff, or Gomori methenamine silver stain was used for the high power examination of all tissue samples.

The patients included in the study were treated according to the Indian Council of Medical Research guidelines.⁵ Liposomal amphotericin B infusion was initiated (10mg/kg/day) for 42 days in patients with cerebral involvement and 5 mg/kg/day for 21 days for patients without cerebral involvement, followed by posaconazole 300 mg bd for the first day and thereafter once daily in both groups until clinical and radiological recovery. Details of presentation, diagnostic imaging, co-morbidities, treatment, and follow-up findings were recorded and analysed.

Statistical analysis

Mean $\pm$ SD, median, range and Wilcoxon sign rank tests were applied for the expression of continuous variables. Counts and percentages in each category and Fisher's exact tests were expressed for categorical variables as appropriate. Survival probability was determined using a Kaplan-Meier plot and the p-value was calculated by log-rank test. The proportional hazard assumption was tested by modelling the log-log of the survival curve using each variable

included as strata, and the proportional hazard assumption was considered un-violated if the curve did not cross all time points. A 95% confidence interval was reported. p-value <0.05 was considered significant. R software version 4.1.2. was used for statistical analysis.

Results

Patient's demographic and Covid-19 history

Seventeen (17) patients were admitted with symptoms of ROCM, and the diagnosis was confirmed by microscopy in 12 patients, culture in 13 patients and histopathology in 12 patients. Seven patients were KOH and culture positive, 7 were culture and histopathological positive and in 5 patients all three tests were positive. Males outnumbered females (male: female ratio 11: 6), age range was 14-71 years with a median of 45 and mean of 45.3.

Table 1: Outcome of demographic, clinical and treatment variables in ROCM patients.

Variables	No of patients	No of deaths	Mortality %
Sex			
Male	11	03	27
Female	06	01	16
Infection Site			
Cerebral	07	04	57
Orbital	07	04	57
Nasal	17	04	23
Palatal	12	02	17
Diabetes status			
Nondiabetic	01	00	00
DKA	03	02	67
Uncontrolled (New onset)	03	00	00
Uncontrolled (Already diagnosed)	10	02	20
Surgical debridement required.			
Yes	09	00	00
No	08	04	50
History of Covid-19			
No history of Covid	02	00	00
Mild Covid	06	01	17
Severe Covid	09	03	33
Steroids used in treatment			
Yes	12	03	25
No	05	01	20
Dialysis required.			
Yes	04	02	50
No	13	02	15

Four patients (23.5%) were diagnosed during active Covid-19 infection and 11 (64.7%) after recovery from Covid-19.

Onset of mucor were mostly 5-50 days (mean 19.7 days) after recovery from Covid.

Disease severity of Covid-19 was mild in six patients (35%) and severe in 9 (53%). A history of Covid-19 was not found in 2 (11.7%) patients – one adolescent and one adult, both of whom were diabetic. (Table 1)

Symptoms and organ involvement

The average duration of symptoms of ROCM at the time of hospital admission was 9.7 days. The common symptoms observed in our study were nasal congestion (100%), coryza (100%) facial pain (82%), epistaxis (70%), chemosis (58%), throbbing pain over eye (52%), extensive headache (47%), ptosis (47%), ophthalmoplegia (41%), proptosis (35%), loss of vision (23%) and convulsion (5%).

All patients with ROCM had nasal involvement (Figure 1), 12 (70.6%) had palatal involvement (Figure 2), and 9 (52.9%) and 7 (41%) had orbital and cerebral involvement. The four patients

(23.5%) who died in the first week after initiation of treatment had extensive cerebral involvement.

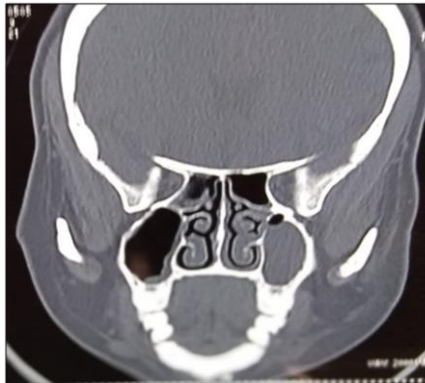


Figure 1: MRI of paranasal sinuses- involvement of bilateral nasal turbinate and right maxillary sinus.



Figure 2: Hard palate involvement, post operative state.

Associated diabetes mellitus (DM)

Among the 17 patients, 16 (94.1%) presented with poorly controlled diabetes mellitus, three (17.6%) were diagnosed with DM during Covid-19, while others gave a long (> 4 years) history of DM. Three patients (17.6%) developed diabetic ketoacidosis.

Treatment received.

Corticosteroids were used to treat 11(64%) patients with Covid-19. Two who had diabetic ketoacidosis and severe disease died. Seven patients received remdesivir while two were treated with tocilizumab.

Orbital exenteration were conducted in two patients. Paranasal sinuses were debrided thoroughly with or without turbinectomy or resection of palate/ orbital wall in nine patients. Repeated surgical procedures were carried out in 3 patients. The total duration of treatment depended on clinical, radiological, and histopathological improvement. Side effects and co-morbidities (mainly diabetes) were aggressively managed. The duration of treatment in ROCM varied between 3-372 days with a median duration of 261 days. Four (29.4%) patients were cured both clinically and radiologically after six months of therapy, 41.1% required an extension of treatment for another three months due to the clinical and radiological persistence of this fungus, while four patients needed treatment for 12 months. The analysis of the prognosis therefore required a longer follow-up.

Survival analysis

Survival rate of overall ROCM was 76.5% with 95% confidence interval (CI-0.587-0.995) (Figure 3).

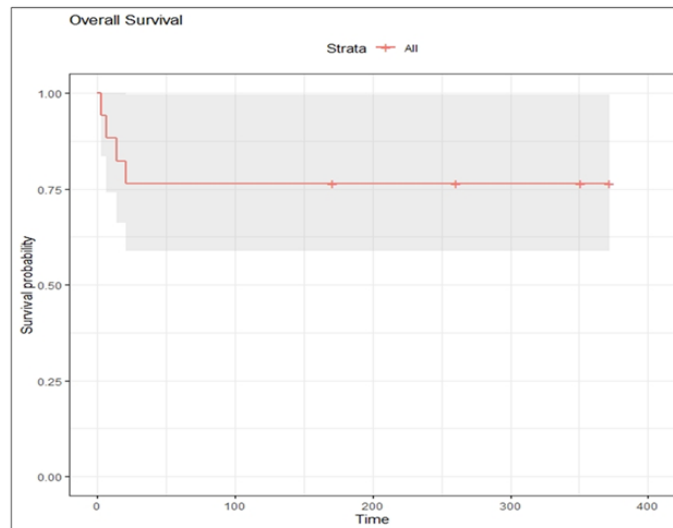


Figure 3: Overall survival probability among ROCM patients.

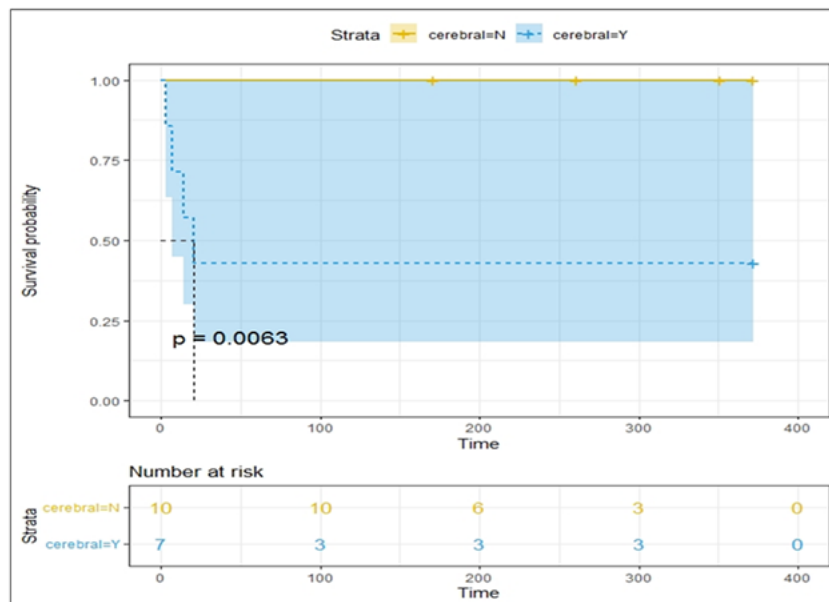


Figure 4: Survival probability in patients with and without cerebral involvement

There appears to be a survival advantage in patients without cerebral involvement compared to patients who had cerebral involvement (Figure 4)

A significant survival benefit was noted in patients who underwent surgical intervention (Figure 5)

The Wilcoxon sign rank test failed to show any statistical significance in

1. total treatment duration and different types of non-cerebral (orbital, nasal, palatal) involvement ($p=0.5173$)
2. treatment duration and severity of (mild, severe) of Covid-19 infection ($p=0.8341$)
3. treatment duration and time gap between onset of symptoms of mucormycosis and hospital admission ($p=0.4211$).

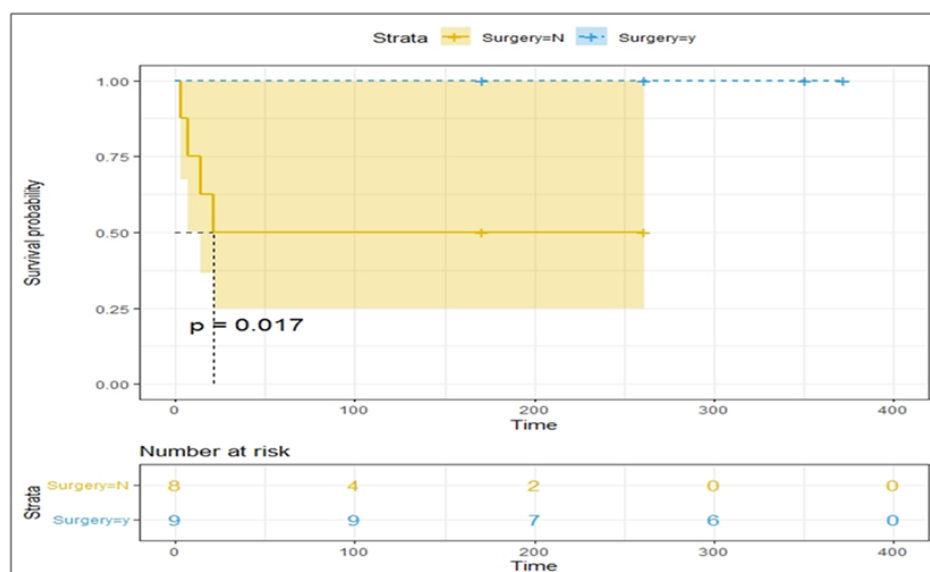


Figure 5: Survival probability among surgically intervened patients

Discussion

The second wave of coronavirus disease in 2021 devastated India with an unexpected surge in mucormycosis which forced the Government of India to declare it as notifiable. Aranjani JM et al (2021) pointed out that ROCM was the most common presentation during the second wave of the covid pandemic with a mortality of 85%.¹ In our study 100% of patients presented with ROCM.

A prospective multicentre study from India concluded that poorly controlled diabetes mellitus (56.8%) and a high association with diabetic ketoacidosis (10% of cases) were the most identified risk factors with a high mortality of around 46%.⁶ Although the current study documented a high association between diabetes (94%) and ROCM, mortality was relatively low (23%). In addition, only 17.6% of patients presented with diabetic ketoacidosis.

Improved survival in COVID-19 with glucocorticoids administered systemically resulted in its rampant prescription which was associated with secondary bacterial or fungal infections. A significant association of mucormycosis with corticosteroid use was shown during the second wave of the pandemic. Eleven patients (64%) received corticosteroids (median duration of six days) for moderate to severe Covid-19 infection in our study. Two of the 11 died and had diabetic ketoacidosis and severe disease. Sen M et al (2021) reported that corticosteroids were advocated in 87% of patients, of whom 21% received it for more than 10 days.⁸ Ravani et al also documented steroid use in 61.2% cases which matches our findings.⁷

The prognosis of this disease depends on associated morbidity. In our study, 41% of patients had cerebral infiltration, and the prognosis was grave when brain tissue was involved. Cerebral involvement as part of the intracranial extension (22.58%), thrombosis of the internal carotid artery (6.45%), and thrombosis of the cavernous sinus (3.22%) has been demonstrated by Ravani et al (2021).⁷ Blood vessel thrombosis and tissue necrosis are basic pathologies during mucormycosis. Antifungal drugs alone cannot cure mucormycosis and they cannot reach the site of active infection in the presence of active tissue necrosis. Therefore, for complete eradication of mucormycosis, adequate debridement of necrotic tissue is of utmost importance. Multiple studies reported that patients who didn't undergo extensive dead tissue debridement

surgery had higher mortality than patients who had surgery.⁹ Similarly, we found that surgery improved survival benefits (Figure 5).

Mortality rates remain high, with figures ranging from 20 to 50% despite intense antifungal therapy and surgical intervention.⁴ Mortality rates also remain high, between 70–90%, for cases of disseminated mucormycosis in patients with critical illness/immune compromised and intracerebral involvement.⁹ Sharma S et al (2021)¹⁰ revealed a favourable outcome in post covid mucormycosis patients with early initiation of anti-fungal treatment along with surgical debridement. We too found a similar outcome of low mortality in this study. The relatively low mortality (23%) in the current study could be attributed to early diagnosis with a high degree of clinical suspicion, initiation of antifungals, and surgical debridement.

The male preponderance documented in our study has been consistently seen in other studies. Statistical significance was, however, not observed among age, gender, COVID-19 positivity, presence of multiple systemic comorbidities, and management modality. Recurrences during the follow-up period in the surviving patients were not detected.

The limitation of our study is that it was a single-centre study. The prominent risk factor for mucormycosis in this study was diabetes, as noted also in Bangladesh and Pakistan with limited data on mucormycosis.² Further studies are required for the comparison of data from countries with a high incidence of diabetes and mucormycosis with that of data from the United States and Europe, where mucormycosis is predominantly encountered among patients with haematological malignancies and organ transplantation.

Conclusion

Physicians caring for patients suffering from ROCM must be aware of the need for completion of treatment which may take up to one year before the patient can be declared infection-free. Close monitoring of clinical improvement and simultaneous radiological and histological clearance of the lesions are important before the stoppage of treatment.

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Authors' contributions:

Dolanchampa Modak- Concept, manuscript writing, data refining, statistical analysis

Subhasish Kamal Guha- Editing, overall guidance

Debajyoti Majumdar- data collection, reference arrangement

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