



Surgical Debridement in Patients of Rhinocerebral Mucormycosis (RCM) Post COVID-19: A Prospective Study

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Abstract

Rhinocerebral mucormycosis (RCM) is an angioinvasive fungal infection, in which infection of the nasal and sinus walls may secondarily invade the orbit, skull base, and brain. RCM carries high mortality up to 46 % in patients with sinus involvement and 62 % in patients with rhinocerebral involvement. The diagnosis of RCM and assessment of the resection margins are based on histopathology, specific cultures, and/or PCR detection of Mucorales species. It was a prospective, longitudinal study conducted under neurosurgery department in Basaveshwara Medical College and Hospital, Chitradurga, Karnataka during 1st May to 30th June 2021. All patients with radiologically, clinically diagnosed & biopsy proven by samples collected intraoperatively are included in the study. Caldwell luc approach was employed for maxillary sinus debridement, FESS for pansinusitis cases & Craniotomy for cases with intracranial involvement. In this study, we found that age, gender, neutrophil counts, monocyte count, ferritin levels, CT severity, diabetic status and usage of steroids and oxygen had a major role in the pathogenesis of mucormycosis. IHC was done and genetic studies were sent. The surgical treatment of RCM requires early diagnosis & aggressive surgical debridement. The outcome of the aggressive debridement was good. The debridement should be continued until clear resection margins are obtained based on the assessment of microscopical findings of hyphae, fungal cultures, and/or fungal DNA detected by PCR.

Keywords: Surgical debridement; Rhinocerebral Mucormycosis (RCM); Post COVID-19

Introduction

The repeated upsurge in the cases of severe acute respiratory syndrome coronavirus-2 infection, or coronavirus disease 2019 (COVID-19), is still causing

havoc worldwide⁽¹⁾. The presence of pre-existing comorbidities such as diabetes mellitus, hypertension, hypothyroidism, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver

disease, and immune-compromised disorders in these patients predisposes them to develop several opportunistic infections that increase the risk of mortality⁽²⁾. Interestingly, uncontrolled diabetes has long been considered to be the most common risk factor associated with mucormycosis⁽³⁾. Mucormycosis represents a life threatening highly invasive and relentlessly progressive group of infections caused by the fungi of order Mucorales, most commonly *Rhizopus oryzae*⁽⁴⁾. Like most invasive fungal diseases, mucormycosis is known to occur in settings of decreased innate immunity. Clinical and experimental data clearly demonstrate that individuals who lack phagocytes or have impaired phagocytic function are at higher risk of mucormycosis⁽⁵⁾. The primary reason that appears to be facilitating Mucorales spores to germinate in people with COVID-19 is an ideal environment of low oxygen (hypoxia), high glucose (diabetes, new-onset hyperglycemia, steroid-induced hyperglycemia), acidic medium (metabolic acidosis, diabetic ketoacidosis [DKA]), high iron levels (increased ferritins) and decreased phagocytic activity of white blood cells (WBC) due to immunosuppression (SARS-CoV-2 mediated, steroid-mediated or background comorbidities) coupled with several other shared risk factors including prolonged hospitalization with or without mechanical ventilators⁽⁶⁾. A total of 24 mucormycosis cases were included in this study.

Materials and Methods

It was a prospective, longitudinal study conducted under Neurosurgery department in Basaveshwara Medical College and Hospital, Chitradurga, Karnataka during the months of 1st May to 30th June 2021. Structured data collection methods were employed.

1. Inclusion Criteria

- (a) All patients who were radiologically and clinically diagnosed to have mucormycosis, who underwent surgical intervention and whose diagnosis was confirmed by biopsy of samples collected intra-operatively.
- (b) All patients who were available for follow up.

2. Exclusion Criteria

- (a) All patients who were not available for follow up.
- (b) Patients with COVID-19 infection diagnosed on the basis of positive Rapid Antigen Test or suspicious of HRCT thorax findings.

Patients who were also in active phase of COVID-19 infection were given parallel treatment for the same. Post operatively, antifungal drugs were given for 3-4 weeks. HRCT reports of all patients were collected for diagnostic purposes and to quantify the CT severity. CT scoring was used to compare

COVID-19 severity with the incidence and severity of Mucormycosis. A unique classification system was devised by our team to grade and assess the severity of Mucormycosis based on the extent of involvement.

I – sinus involvement

II – sinus involvement along with extension to the skull base

III – sinus involvement, extension to skull base, along with orbital involvement

IV – intracranial extension

‘m’ symbolizes metastasis of Mucormycosis through the blood in the form of septic emboli

CT PNS, CT brain and MRI PNS, orbit and brain along with post operative tissue sample histopathology and KOH mounts were used for initial diagnosis and follow up for all patient of Mucormycosis. Surgical strategy was based on radiological characteristics of each case. Caldwell luc approach was employed for maxillary sinus debridement whereas FESS was employed for pansinusitis cases. Craniotomy was preferred for cases with intracranial involvement.

Results

Table 1. Age distribution of the study population

Age	Number of patients
<30	1
31-40	8
41-50	7
51-60	6
>60	2

From the above data, 87.5% of the study participants lie in the 31-60 years age range with maximum (33%) in 31-40 years age range.

Table 2. Gender distribution of study population

Gender	Number of patients
Males	21
Females	3

From the above data, 87% of the study participants were males while 13% were females.

Majority of the Mucormycosis patients show normal to elevated total white cell counts with 34% in the 9001-11000 range, with 25% above 14000 cells/mm³.

Above data shows that 37.5% of the patients had neutrophil counts in 81-90% range while another 37.5% of the patients were in 71-80% range

Table 3. Total leucocyte counts of study population

TLC Counts (cells/mm ³)	Number of patients
<6000	1
6001-7000	1
7001-8000	2
8001-9000	3
9001-10000	4
10001-11000	4
11001-12000	2
12001-13000	0
13001-14000	0
14001-15000	3
15001-16000	0
16001-17000	3
>17000	1

Table 4. Neutrophil counts of study population

Neutrophils (% of TLC)	Number of patients
<60	2
61-70	4
71-80	9
81-90	9

Table 5. Lymphocyte counts of study population

Lymphocytes (% of TLC)	NUMBER OF PATIENTS
5-9.9	4
10-14.9	8
15-19.9	3
20-24.9	5
25-29.9	2
30-34.9	0
35-39.9	2

Lymphopenia is the predominant finding in the laboratory data of Mucormycosis, with 33% of the cases having 10-14.9%, 21% having 20-24.9%, 17% having 5-9.9%, 8% of the cases with 25-29.9% and 35-39.9% each.

Majority of the cases of Mucormycosis have elevated serum ferritin levels with 25% of the cases coming under the range of 301-500ng/ml, 17% coming under the range of 501-700 and 701-900 ng/ml each, 16% cases with very high ferritin levels and only 13% of the cases with normal levels.

Table 6. Monocyte counts in study population

Monocytes	Number of patients
1-3.9	8
4-7.9	15
8-11.9	1

Table 7. Serum ferritin levels in mucormycosis patients

Serum ferritin levels (ng/ml)	Number of patients
100-300	3
301-500	6
501-700	4
701-900	4
901-1100	1
1101-1300	2
1301-1500	2
>1501	2

Table 8. D – Dimer levels in study population

D – Dimer levels (ng/mL)	Number of patients
<100	4
101-300	10
301-500	5
501-700	3
>700	2

D-dimer values are elevated in majority of the patients with 83% of the cases lying under the range of 101-1000 ng/ml and only 17% lying under the normal range

Table 9. Serum sodium levels

Serum Sodium (mEq /L)	Number of patients
120-125	2
126-130	0
131-135	13
136-140	7
>140	2

Majority of the patients have levels of sodium that lie under the range of 131-135 meq/L with 54% having marginally reduced levels and only 29% in the normal range

66% of the cases have moderate COVID disease, whereas only 16.6 % of the cases have severe COVID diseases and 8.3% of the cases have mild COVID infection.

Table 10. CT severity score of mucormycosis patients during COVID 19 illness

CT Severity score (Out of 25)	Number of patients
3-5	2
6-10	6
11-15	14
16-20	1
N/S	1

Table 11. Diabetes status of mucormycosis patients

Diabetic status (Based on HbA1C and FBS)	Number of patients
Diabetic, on medication	19
Diabetic, not on medication	5
Non – diabetic	0

Table 12. Steroid prescription status during COVID 19 illness of patients with mucormycosis

Steroid prescription status during Covid-19 illness	Number of patients
YES	22
NO	2

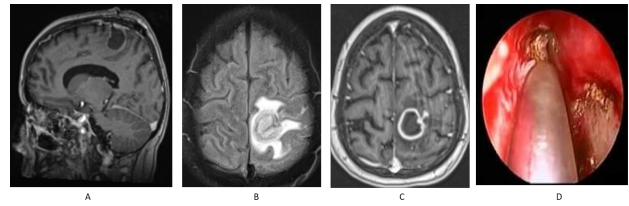
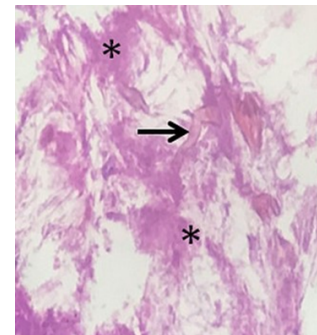
Table 13. Oxygen usage status during COVID 19 illness in mucormycosis patients

Oxygen usage status during Covid-19 illness	Number of patients
YES	17
NO	7

No mortality was reported in our study and clinical outcome of 22 patients (91.66%) was good. 2 patients (8.34%) had headache and blurring of vision but no permanent loss for any higher function was observed after surgery in our study. In this study, we found that age, gender, neutrophil counts, monocyte count, ferritin levels, CT severity, diabetic status and usage of steroids and oxygen had a major role in the pathogenesis of mucormycosis.

Discussion

A total of 24 cases of Mucormycosis were analyzed in this study. There is clear distinction in the gender involvement of Mucormycosis with 90% of the patients being male and 10% being females. This implies that male gender is a clear predisposing factor for Mucormycosis. We hypothesize that in the Indian settings, this could be due to male

**Fig 1. A) MRI of RCM 1, B) MRI of RCM 2, C) AXIAL image of RCM 3, D) ENDOSCOPIC image of RCM (while Debridement)****Fig 2. HPE of Mucormycosis**

specific risk factors such as smoking, alcohol intake that affect the local immunity of the paranasal sinuses, thus causing increased chances of mucormycosis when associated with severe COVID infection even though this specific data wasn't available. This result is in concordance with other studies^(5,7). On analysis of the age of the patients suffering from Mucormycosis, it was found that the age range of 41-50 had the maximum number of cases with the mean age being 45.9 years. This result coincides with other studies^(8,9). We analyzed the total count, neutrophil count, lymphocyte and monocyte values for all the patients and reached to a conclusive result that majority of the patients with Mucormycosis have an increase of neutrophil count with 38% of them lying in the range of 81-90%. This result coincides with another study⁽¹⁰⁾. Monocyte counts were elevated, either marginally or significantly in majority of the patients with mucormycosis. On the other hand, lymphocytes were well within the normal range in majority of the cases, thus suggesting that lymphocytes may not have a pivotal role in the pathogenesis of Mucormycosis. This result is in concordance with another study regarding the same⁽¹¹⁾. Serum ferritin values of Mucormycosis patients during their COVID illnesses were analyzed and it was found that serum ferritin levels were markedly increased with majority of the values ranging between 700-900 ng/ml. This suggests a definite relation between elevated levels of serum ferritin and occurrence of Mucormycosis in the post COVID period. This is in concordance with other studies⁽⁵⁾. It was also observed that majority of Mucormycosis patients had

deranged electrolytes, especially sodium levels with majority of them coming under the range of 131-135meq/L. There are not many studies conducted that have shown a link between marginally low sodium levels and mucormycosis and further research is required in this area to substantiate sodium levels as a useful prognostic indicator for Mucormycosis⁽¹²⁾. Waiting for cultures is impractical and may lead to an inadvertent delay in the initiation of treatment. If a clear clinical picture of mucormycosis exists, positive KOH mounts may be sufficient for initiating treatment. HRCT severity score of all the patients were collected and it was observed that majority of the patients had severe form of the disease, i.e., >15/25 severity score, following or during which, they developed Mucormycosis as seen in other studies^(1,13). We analyzed the history, FBS and HbA1c levels of all our patients and the results were conclusive. Almost all our patients were diabetic, majority of them were on medication with urine ketone bodies positive in some cases. This suggests a probable link between diabetic status and occurrence of Mucormycosis as seen with other studies^(5,14,15). In our study, all our patients had been treated with steroids and oxygen during the course of their COVID illness as was seen in other studies^(16,17). However, in a parallel study that we conducted that is yet to be published, wherein we compare this data with control group of patients with COVID, it was found that despite the same treatment, they did not develop mucormycosis.

Conclusions

Early diagnosis of COVID-19 mucormycosis through sharp clinical acuity and initiation of early surgical intervention seems to be the key to control this disease burden and prevent its numerous debilitating complications. The surgical treatment of RCM requires early diagnosis, aggressive surgical debridement, and early reconstructive surgery. The debridement should be continued until clear resection margins are obtained based on the assessment of microscopical findings of hyphae, fungal cultures, and/or fungal DNA detected by PCR. Considering the good clinical outcome achieved in our study with prompt and aggressive management, the significance of high degree of clinical suspicion, the earliest recognition and treatment of mucormycosis with aggressive surgical debridement in combination with antifungal medication cannot be overstated.

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