Research

Surgical management of COVID-19 associated rhino-orbito-cerebral-mucormycosis (Ca-Rocm): A single centre experience

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Abstract: COVID-19 associated rhino-orbito-cerebral-mucormycosis (CA-ROCM) is a fulminant and life-threatening disease. Surgical intervention and prompt antifungal therapy are the mainstays of treatment. This is an observational, retrospective and a single centred study, on 24 active COVID-19 and 50 post-COVID-19 patients, with ROCM respectively. The study was carried out from a period of May 1st 2021 till July 15th 2021 at a tertiary care hospital in South India. Patients were followed up for a period of 12 months for survival. A total of 74 COVID-19 patients with ROCM were included in our study. Of which 24 were active COVID-19 patients and 50 were post COVID-19 patients. The median age at presentation was 50 years, ranging from 31-75 years, 46 (62.2%) patients were males and 28(37.8%) were females. The average days from the diagnosis of COVID-19 to the appearance of symptom indicative of ROCM was 21.9 days, ranging from 4-51 days. Majority of patients belonged to stage IIC (43.24%) followed by stage IIB (23%) according to the staging system. Patients with >stage 3C had poor prognosis. The mortality was 8.1%. 8 patients underwent surgery for recurrence in the follow-up period. Early diagnosis, surgical debridement, anti-fungal treatment and close monitoring are the keys to management of CA-ROCM. A staging system aids in formulating an effective surgical plan for better survival outcomes.

Keywords: COVID-19; mucormycosis; post-COVID; surgical staging

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1. Introduction

Mucormycosis is a progressive, angio-invasive fungal infection caused by the fungi belonging to group Mucorales. Its occurrence was rare in the past, but complications lead to life-threatening conditions. Thrombosis of blood vessels and subsequent tissue necrosis due to angio-invasion by the fungal hyphae are the hallmarks of Mucormycosis. Recently, India witnessed an upsurge of ROCM cases in COVID-19 affected patients. Published data revealed that 71% of COVID-19 associated Mucormycosis (CAM) patients were from India and over 94% had underlying uncontrolled diabetes [1]. During the second wave of COVID-19 infection by B.1.617.2 (Delta) variant, several states in India declared CAM as an epidemic [2].

The prevalence of mucormycosis varies from 0.005 to 1.7 per million population on a global level [3]. Whereas in India, the estimation is 140 per million population. Delayed diagnosis as an important prognostic factor in in determining the outcomes of CAM [4]. The global guidelines by The European Confederation of Medical Mycology (ECMM) with the Mycoses Study Group Education and Research Consortium (MSG ERC) highly recommends early and extensive surgical intervention [5]. With the alarming rise of

COVID associated Rhino-Orbito-Cerebral-Mucormycosis (CA-ROCM) patients, the management of CA-ROCM patients was a challenge. Hence, we adopted a grading system for surgical treatment of CA-ROCM patients. In this paper, we describe our experience and the outcomes of surgical intervention in COVID-19 patients associated with ROCM.

2. Materials and Methods

This was an observational study and we conducted this study on 74 patients who developed ROCM during active COVID-19 and after COVID-19 infection. The study was carried out between May 1st 2021 to 15th July 2021 at a tertiary care centre in South India. Demographic details, vaccination status, average days between COVID-19 diagnosis and the onset of symptoms suggestive of ROCM, clinical features of ROCM, co-morbidities, nasal endoscopy, microbiological, pathological and radiological findings, medical and surgical treatment were evaluated. Patients in paediatric age group or with incomplete data and who were not willing were excluded from our study.

2.1. ENT Protocol

A detailed clinical history was obtained from patients. Diagnostic nasal endoscopy was done for all patients with ROCM. Nasal biopsy from the affected nasal cavity (tissue from nasal eschar/affected mucosa/necrotic tissue from affected cavity) was taken and sent for Potassium hydroxide (KOH) staining and microbiological examination. All patients underwent radiological assessment.

MRI was the primary imaging modality. Patients with suspected intra-orbital, neurovascular or intracranial involvement underwent contrast enhanced magnetic resonance imaging (MRI). Medical treatment and surgical planning were framed based on the grading of the disease.

Pre-operative evaluation was performed for all patients undergoing surgery. All patients underwent either one or a combination of the following surgeries: endoscopic debridement/TRAMB/paletectomy/transpterigoid/cribriform/infratemporal/orbital decompression/frontal fenestration/orbital exenteration. All patients were administered Amphoterecin-B cumulative dose of 3 g during hospitalization and were discharged on Posaconazole tablets 300 mg for 45 days.We had challenges of Amphotericin B crisis ,so patients were even maintained on posaconazole for 2 months. Here we followed three modalities to manage the disease i.e., anti – fungal treatment, strict glycaemic control and surgeries.

2.2. Case definition

Active COVID-19 patients were defined as patients with laboratory confirmation of SARS-CoV-2 (by RT–PCR) at presentation [6]. Post COVID refers to patients recovered from COVID-19 infection after 3 months and are currently RT–PCR negative for SARS–CoV2 and positive for antibody [7]. The time limit of three months was taken as per the widely accepted definition of post-acute COVID-19 syndrome. Patients with mild COVID-19 infection were managed in home isolation. Whereas patients with moderate to severe disease were managed in hospital.

2.3. Statistical analysis

Statistical analysis was performed using SPSS (Version 23). The continuous variables were expressed as mean and standard deviation. Categorical variables were expressed as frequency and percentage. Independent 't'-test was used to find the significance difference between groups. Correlations relationship between two variables analysed by applying Person's coefficient. Chi-square test and fisher's exact test were used to find out association between the categorical variables.

3. Results

A total of 74 COVID-19 patients with ROCM were included in our study. The median age at presentation was 50 years, ranging from 31–75 years and 46(62.2%) patients were males whereas 28(37.8%) were females. The demographic profile and clinical characteristics of ROCM patients are presented in Table 1. Among the 74 patients, 24 active COVID-19 patients had been diagnosed with ROCM and 50 patients presented with ROCM in post COVID-19 infection period.

A 70 patients were hospitalized for COVID-19 management whereas four patients were managed in home isolation. Among hospitalized patients 46 patients are males (65.7%) and 24 patients (34.3%) are females and all 4 home quarantined patients (4) are females and this is statistically significant. The average days from the diagnosis of COVID-19 to the appearance of symptom indicative of ROCM was 21.5 days, ranging from 4–51 days. Seven patients (9.5%) had received first dose of COVID-19 vaccination and one patient (1.4%)completed vaccination and this is statistically significant in this study. All patients eventually had diabetes either pre COVID or developed diabetes post COVID infection, 7(9.4%) patients had systemic hypertension and one patient (1.4%) had coronary artery disease. Among the patients with diabetes, 66.2% patients had prior history of diabetes mellitus whereas 33.8% patients were detected to have diabetes mellitus during the COVID-19 infection and in the post COVID-19 infection period.

Table 1: Baseline clinical characteristics of CA-ROCM patients

Clinical parameter	**Value n(%)**
Age, median (IQR) years	50 (31-75)
Gender	
Male	46 (62.2)
Female	28(37.8)
COVID-19 status	
Active	24 (32.4)
Post COVID	50 (67.6)
Treatment status	
Home quarantine	4(5.4)
Hospitalization	70(94.6)
Days between COVID-19 diagnosis and onset of symptoms, median (IQR) days	21.9 (4-51)
COVID-19 Vaccination status	
No dose	66 (89.2)
First Dose	7(9.4)
Two Doses	1(1.4)
Co-morbid conditions	
Diabetes Mellitus	74(100)
Hypertension	7(9.4)
Coronary Artery Disease	1(1.4)
Diabetes Mellitus	
Known to have Diabetes	49(66.2)
Post COVID (New Onset Diabetes)	21(28.4)
Prediabetes	4(5.4)

Data are expressed as n(%) unless otherwise indicated.CA-ROCM ,COVID-19 associated rhino-orbito-cerebral-mucormycosis.

A 84% of patients predominantly presented with facial pain, 57% patients had headache, 44% patients had orbital pain and/or swelling, 32% had facial numbness, 11% had loose teeth. Other symptoms include cheek swelling (5%), proptosis (5%). ptosis (5%), restricted EOM (7%), palatal involvement (4%) and impaired/loss of vision (3%).Majority of patients belonged to stage IIC (43.2%) followed by stage IIB (23%) according to the staging system illustrated in Table 2.

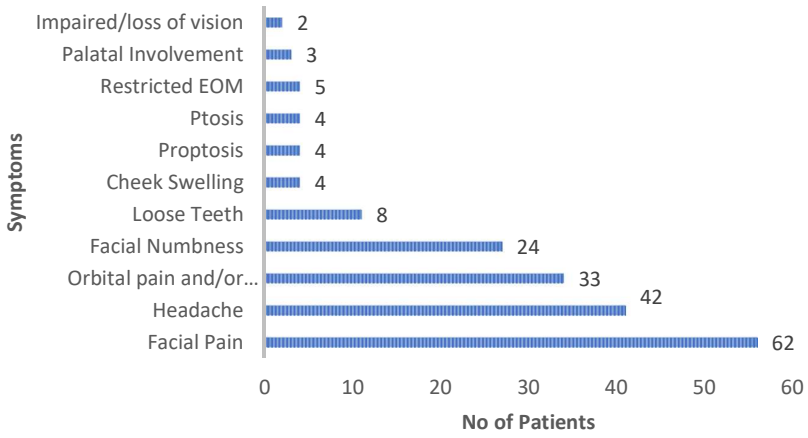

Fig. 1. Clinical featured of ROCM with COVID-19 infection.

Table 2: COVID-19 patients with ROCM according to the staging system

Stages	Number of patients n (%)
2A	1(1.4)
2B	17(23)
2C	32(43.2)
2D	2(2.7)
3A	3(4.1)
3B	6(8.1)
3C	3(4.1)
4A	5(6.8)
4B	1(1.4)
4D	4(5.4)

Six patients died due to complications of mucormycosis, with a mortality of 8.1%. 5 patients died in the postoperative period and they had intracranial involvement, one patient died in the follow-up period. We did follow-up of our patients for 12 months and eight had recurrence requiring surgical debridement.

4. Discussion

Mucormycosis is a fulminant and life-threatening fungal infection. India has witnessed an alarming rise of ROCM cases in the second wave of COVID-19 pandemic. According to a study conducted by White et al, the incidence of invasive fungal infection in COVID-19 patients was 26.7% [8].

The median age of presenting was 50 years, ranging from 31-75 years in our study. We observed a slightly higher proportion of patients in younger age group between 31 and 50 years. The possible scientific explanation for affinity of SARS CoV-2 towards young people remains unclear. The male population (62.2%) was predominantly higher in our study when compared to females (37.8%).

In this study, all patients eventually had diabetes either pre COVID or developed diabetes post COVID infection. Among the diabetic population, 66.2% patients had prior history of diabetes mellitus and these patients had uncontrolled diabetes. A 33.8% of patients comprised of recently detected diabetic patients and diabetes diagnosed during COVID-19 infection and post infectious period. A large number of patients were found to have diabetes during the active COVID-19 infection and in the post infectious period. The SARS CoV-2 virus inflicts direct injury to pancreatic cells, thus COVID-19 affected patients have the propensity to develop diabetes. Hence the patients recovering from COVID-19 infection should be monitored for diabetes.

The median time interval between COVID-19 diagnosis and the onset of mucormycosis disease was 21.5 days. Facial pain was the most common manifestation, present in 84% followed by headache in 57% patients, orbital pain and/swelling in 44% patients and loose/mobile teeth in 11% patients. Other manifestations include proptosis, ptosis, restricted EOM, palatal involvement and impaired/loss of vision. According to the global guidelines for diagnosis and management of mucormycosis, suspicion of ROCM warrants CT scan or MRI scan of nose, paranasal sinuses, orbit and brain [9]. MRI is preferred over CT if orbit or brain involvement is suspected. Biopsy followed by surgical intervention is recommended. Mucormycosis is characterized by angio-invasion with infarction and the treatment is radical surgical removal of the infected tissue and timely antifungal therapy. In a study conducted by Roden et al, reports suggest that surgical excision of infected tissue improved survival rates of up to 70% when combined with prompt antifungal therapy [10]. In our study, we found a high proportion of patients in stage IIC 43.2% followed by IIB 23%. The mortality rate was 8.1%. In our study, we observed a slightly lower mortality when compared to a study conducted by Vaid et al. [11]. This may be attributed to early diagnosis and timely intervention of surgery in combination with antifungal therapy [12]. However, the outcomes depend on the site of involvement and the time of initiation of treatment [13-16]. We initiated liposomal amphotericin B/conventional amphotericin B/lipid emulsion for our patients. In view of amphotericin B crisis, we treated our patients with Posaconazole [13]. Six patients had lost their lives, of which one patient who had stage IIIC underwent surgical debridement in the follow-up period. One patient had stage IVA and the remaining four patients had stage IVD disease. Honovar et al proposed a four stage grading system for precise anatomical localization of critical areas of disease progression [17]. Higher stages indicate extensive involvement and requires aggressive surgical intervention. Due to the aggressive and potentially fatal nature of the disease, the most important factor in determining the outcome of ROCM was early diagnosis [12]. A 52(70.3%) patients were in early stage (stage II) and 22(29.7%) patients were stage III and IV. 28% of patients beyond stage II indicate the need for stringent follow-up protocols to monitor disease progression and survival. The staging system aided in the evaluation of disease pattern. We did follow-up of our patients for 12 months and eight had recurrence requiring surgical debridement. 5 patients belonged to stage 2C, one patient in stage 3A, 3B and 3C.

4.1. Limitation

This is a retrospective, single centre study. The need for long-term follow-up of patients is imperative to evaluate the disease progression.

5. Conclusion

ROCM in COVID-19 was a formidable challenge. Increasing trends of ROCM in post-COVID patients was recognized in the second wave. High index of suspicion, establishment of early diagnosis, timely surgical intervention, appropriate antifungal therapy and glycaemic control play crucial roles and are the keys to favourable outcomes. A multidisciplinary approach and strict follow-up protocols are essential to improve the outcomes of Mucormycosis in COVID-19 patients and Long COVID patients.

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