ORIGINAL ARTICLE

RHINO-ORBITO-CEREBRAL MUCORMYCOSIS (ROCM), GRAY AREAS OF MANAGEMENT - A STUDY PRESENTING HIGH INCIDENCE WITH COVID-19

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Background: Rhino-Orbito-Cerebral Mucormycosis is caused by fungi belonging to the Mucorales family, with *Rhizopus arrhizus* being the most common causative agent. It is a fatal and debilitating condition that is prevalent in developing countries, with a mortality rate ranging from 50% to 85%, reaching 100% in disseminated or untreated cases. The diagnosis is based on tissue histopathology and culture confirmation. Some studies have assessed the efficacy of antifungal regimens. Limited knowledge of the disease, its diverse presentations, delays in early diagnosis, and insufficient efforts to identify the root cause pathogen are key challenges highlighted in the review. **Methods:** A retrospective study was conducted at Sheikh Zayed Hospital in Lahore, enrolling patients with ROCM from June 2018 to August 2022. Data from patients admitted over five years was collected and analyzed. All patients underwent surgical debridement and received intravenous Amphotericin. A definitive diagnosis was made through microscopic examination of necrotic tissue and cultures. **Results:** Diabetes mellitus was a common factor among all patients, with a few cases also involving end-stage renal disease and iatrogenic immunosuppression in post-transplant and chemotherapy patients. The study reported a high incidence of ROCM among COVID-19 patients with diabetes mellitus, emphasizing challenges related to treatment costs and patient compliance. Additionally, the one-year survival rate of patients was evaluated. **Conclusion:** The study concluded that the primary causes of morbidity and mortality included the diversity of disease presentations, missed or delayed diagnoses, inadequate laboratory facilities, high treatment costs, unavailability of antifungal medications, drug toxicity, prolonged hospital stays, and poor follow-up. These issues, along with the emergence of new Mucorales species and drug resistance, underscore the need for focused interventions to address these gray areas.

Keywords: Gray areas; Mucormycosis; Mucorales; *Rhizopus arrhizus*; ROCM

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INTRODUCTION

Rhino-Orbito-Cerebral-Mucormycosis, a rare but potentially fatal fungal infection, has recently emerged as a major concern worldwide due to the COVID-19 pandemic. This disease is caused by fungi belonging to the Mucorales family, which includes approximately 27 species that can cause human infections.[1] *Rhizopus arrhizus* is the most common causative agent of mucormycosis globally. ROCM is a type of mucormycosis that affects the sinuses, nasal cavity, and the brain. The disease is fatal, and debilitating, and can cause loss of organs, poor cosmetic results, and financial burden on the patient's family. The mortality rate is high, ranging from 50% to 85%, and even up to 100% in disseminated and untreated diseases.[2] The exact reasons for the increased incidence of ROCM among Covid-19 patients are not yet clear. However, several factors may contribute to the susceptibility of these patients to fungal infections, including the use of immunosuppressive medications, uncontrolled diabetes, and prolonged hospitalization.[3] The diagnosis of ROCM depends on the identification of organisms by tissue histopathology and culture confirmation. Despite recent advances in the management, the treatment of mucormycosis remains challenging, particularly in cases involving the rhino-orbito-cerebral region. The purpose of this case series is to present a literature review and to highlight the gray areas in the management of rhino-orbito-cerebral mucormycosis. The diagnosis of mucormycosis is based on clinical presentation, radiographic findings, histopathology, and culture confirmation. Early detection is vital for the successful management of mucormycosis. However, the diversity of clinical presentations can lead to diagnostic challenges.[3] In some cases, the diagnosis may be delayed due to the non-specific symptoms of the disease. The most diagnostic feature of mucormycosis is

the presence of characteristic broad, non-septate hyphae in tissue sections using histopathology. The diagnostic gold standard is positive culture and cultures of the organism can also be obtained from tissue specimens, blood, and other bodily fluids. However, obtaining a positive culture can take several days, and cultures are negative in approximately 30% of cases. Imaging studies, such as CT and MRI, can help in the early diagnosis of mucormycosis. CT scans may reveal a soft tissue mass, bone erosion, and opacification of the paranasal sinuses. MRI can provide detailed knowledge of the extent of the disease, including the involvement of adjacent structures, such as the orbit and brain. The management of mucormycosis involves a combination of surgical debridement and antifungal therapy. Early and aggressive surgical debridement is crucial for the successful management of mucormycosis.[4] The goal of surgery is to remove all infected necrotic tissue and debris. This can help to reduce the fungal burden and enhance the efficacy of antifungal therapy. The choice of antifungal therapy for ROCM is controversial. The primary antifungal agent used in the treatment of ROCM is Amphotericin B. However, the total dose and duration of treatment with amphotericin B are still controversial. Some studies suggested that high doses of amphotericin B are related to improved outcomes in patients with ROCM. However, high doses of amphotericin B can also cause significant side effects, such as renal toxicity and electrolyte imbalances. In recent years, there have been anecdotal reports of using combination therapy, such as amphotericin B with either posaconazole or an echinocandin, such as voriconazole. However, there is not a single randomized trial that assesses the efficacy of antifungal regimens in the treatment of ROCM. The optimal duration of therapy with antifungal agents is also uncertain. Despite recent advances in the management of ROCM, there are still many gray areas in the diagnosis and treatment of this disease, especially in cases involving the rhino-orbito-cerebral region. One of the major challenges in the management of mucormycosis is the diversity of clinical presentations. In some cases, the diagnosis may be delayed due to the non-specific symptoms of the disease, which can mimic other conditions such as bacterial sinusitis or viral infections.[5] Another gray area in the management of mucormycosis is the role of adjunctive therapies. For example, hyperbaric oxygen therapy has been suggested as a potential adjunctive therapy for ROCM, based on the rationale that increasing tissue oxygenation can improve the efficacy of antifungal agents. However, there are limited studies on the use of hyperbaric oxygen therapy in the management of ROCM. The optimal duration of antifungal therapy is also uncertain. Some experts recommend continuing antifungal therapy until there is radiological evidence of resolution of the disease, while others suggest a shorter course of therapy, especially in cases where surgical debridement has been successful.

MATERIAL AND METHODS

This retrospective study was conducted on patients diagnosed with Rhino-Orbito-Cerebral Mucormycosis (ROCM) from June 2018 to August 2022, who were admitted to the Department of Otorhinolaryngology and Head & Neck Surgery at Shaikh Zayed Hospital, Lahore. Data was collected on patient demographics, including age, sex, and underlying medical conditions. The incidence and causes of ROCM were recorded, along with clinical presentation, radiological findings, diagnostic methods, treatment modalities, and outcomes, based on medical records. Magnetic resonance imaging (MRI) was utilized alongside standard sinus CT scans in patients with clinical suspicion of intraorbital or intracranial disease extension. These imaging techniques were employed not only for initial diagnosis but also for follow-up. A definitive diagnosis was made through microscopic examination of necrotic tissue and culture analysis. All patients underwent treatment with Amphotericin B and extensive debridement via a lateral rhinotomy approach and/or endoscopic disease clearance (Modified Denker's approach). Descriptive statistics, including mean ± SD, were used to present the data, which was analyzed using SPSS version 23.0 software.

RESULTS

Our study aimed to investigate the incidence and management challenges of ROCM in patients with Covid-19. The study included 60 patients, out of which 33 were male and 27 female. The ages of the patients were between 18–81 years. Out of the 60 patients, 50 were diagnosed with diabetes mellitus(DM), 47 out these were patients of type 2 DM), and 3 had type 1 DM

Furthermore, 1 patient had DM + chronic kidney disease + hypertension, 1 patient with DM+ Chronic obstructive pulmonary disease (COPD) + chronic liver disease (CLD), 1 patient had DM + chronic kidney disease(CKD) + CLD, and 1 patient had DM and hypothyroidism. Only two patients had none of above predisposing factors and only gave recent history of tooth extraction. Among the patients, 37 underwent lateral rhinotomy, 8 underwent endoscopic clearance, and 3 patients underwent palatal debridement only. However, 12 patients refused the treatment. All were offered amphotericin B injections out of which 33 afforded liposomal amphotericin B and 13 patients got standard Amphotericin injection (Non liposomal). The total cost of the treatment ranged from 100,000 Pakistani rupees (PKR) upto 15 million PKR. Among the patients, 25 had a procedure cost of 100,000 PKR to 100,0000 PKR, 13 had a cost of 1100000 PKR to 2000000 PKR , and 1 patient had a cost of 5000000 PKR . Two patients had a cost of

15000000 PKR . In 19 patients we could not retrieve the cost due to non-availability of data and poor followup by patients. In terms of patients socioeconomic status, 9 patients were farmers, 9 were businessmen, and others were laborers, job holders, shopkeepers, and government servants. The study highlights the high incidence of ROCM in COVID-19 patients along with DM and its management challenges, particularly in terms of cost and patient compliance. After 1 year 25 patients out of 60 were alive with adequate follow-up. 12 patients left without treatment against medical advice with miserable conditions because of non-affordability, refusal to give high-risk consent to undergo surgery, and poor and guarded prognosis explained to them on initial presentation. 10 patients lost follow-up, and 13 patients died during treatment within one year.

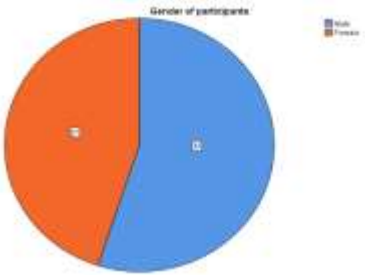

Figure-1: Gender distribution

The pie chart shows the gender distribution of 60 respondents. Of the respondents, 55% (33) are male and 45% (27) are female.

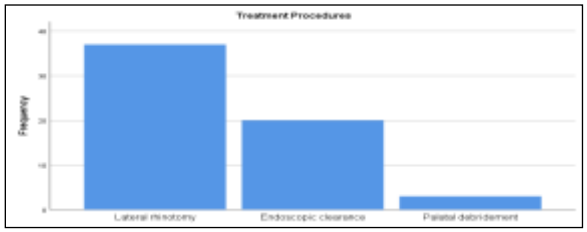

Figure-2: The Frequency distribution of treatment procedure

The bar chart shows the frequency distribution of treatment procedures for the patients. 61.7% underwent lateral rhinotomy, 33.3% underwent endoscopic clearance and 5% underwent palatal debridement procedure.

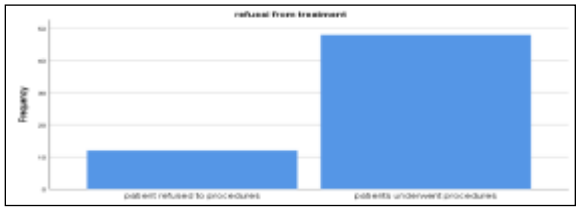

Figure-3: The Frequency distribution of treatment refusal

The bar chart shows the frequency distribution of patient refusal for the procedure. 61.7% underwent lateral rhinotomy, 33.3% underwent endoscopic clearance and 5% underwent palatal debridement procedure.

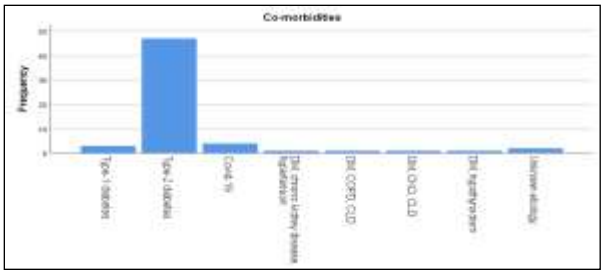

Figure-4: The Frequency distribution of Co-morbidities along with Covid-19

Out of the 60 patients, 47 were diagnosed with type 2 DM and 3 with type 1 DM among them, 4 were isolated covid-19+. Furthermore, 1 patient had DM + chronic kidney disease + hypertension, 1 patient with DM+ COPD + CLD, 1 patient had DM + CKD + CLD, 1 patient had DM and hypothyroidism and two patients reported unknown aetiology.

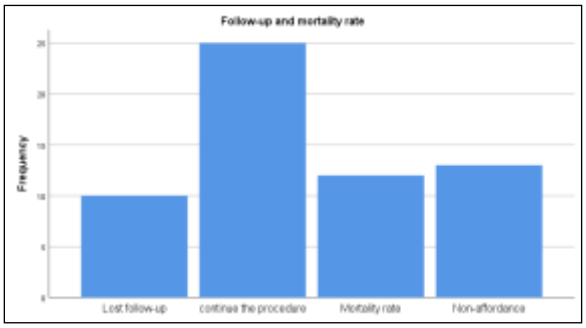

Figure-5: The Frequency distribution of follow up & mortality rate

The bar chart shows that out of the 60 patients, 10 patients lost follow-up, 25 patients continued the whole procedure, 12 patients died during the follow-up, and lastly, 13 patients left due to non-affordance issues. The following images show the examination, investigation, management plan, and treatment of before and after procedure of the patients.

Figure-6: Oral cavity Examination

Erosion or necrosis of hard palate, oroantral fistula may be present.

Figure-7: Nasal Examinations

may show thick black crusting, used as a sample for microscopy

Figure-8: On Face Examination
Swelling of the right cheek with right-sided facial palsy.

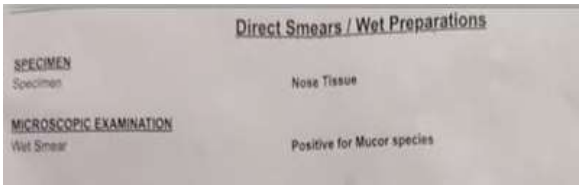

Figure-9: Microscopic Examination report of one of the patients shows positive results for mucor species

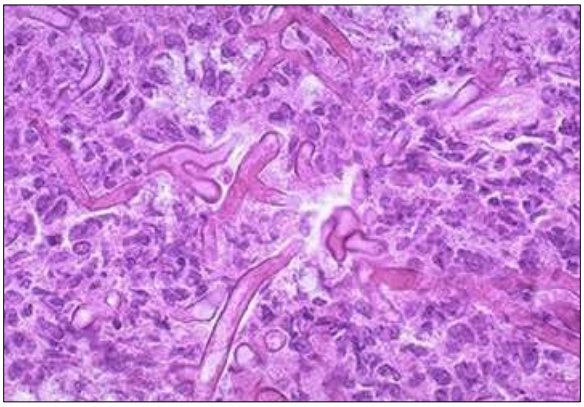

Figure-10: Microscopic View
Broad nonseptate thick hyphae of mucormycosis

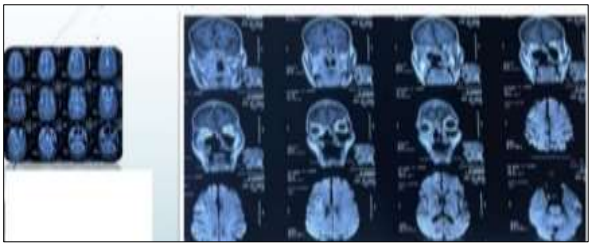

Figure 11: MRI Brain,Nose &Paranasal sinuses
Fungal growth, bony erosions in nose,paranasal sinuses ,orbital invasion

Figure-12: Surgical incision for debridement
Most commonly used incision for lateral rhinotomy.

Figure-13: Images of few patients before & after treatment

DISCUSSION

Our study presents high incidence of ROCM with COVID-19 and its management challenges. It highlights the increased prevalence and the management challenges. The study included 60

patients and found that 50 of them had diabetes mellitus, indicating that DM is a major risk factor for ROCM in COVID-19 patients. The study also revealed that the management of ROCM is challenging due to the high cost of treatment and patient compliance issues. Patel A *et al* [7] also found similar findings in their study on ROCM in COVID-19 patients.

Several other studies have shown an increased frequency of ROCM in COVID-19 patients, particularly with diabetes mellitus. A study[8] showed the frequency of ROCM in COVID-19 patients at 17.6%, and DM was the most common comorbidity observed in these patients. Another retrospective study by Singh AK *et al*[9] showed an incidence of ROCM in COVID-19 pa tients of 5.5%, and diabetes mellitus was again found to be the most common comorbidity.

The management of ROCM requires a multidisciplinary approach, including diagnosis, surgical debridement, and antifungal therapy.[10] However, the high cost of treatment is a significant barrier to ROCM management, particularly in lower and middle-income nations.[11] A study by Muthu V *et al*[11] reported that the cost of treatment for ROCM in India ranges from INR 100,000 to INR 10,000,000 (approximately USD 1,400 to USD 140,000), depending on disease severity and the duration of hospitalization. This cost is prohibitively high for most patients in lower- and middle-income nations, where the majority of ROCM cases occur.

Patient compliance with long-duration treatment is another significant challenge in ROCM management.[12] A study[12] reported that noncompliance with antifungal therapy is common in ROCM patients, particularly in those with a poor socioeconomic status. The reasons for noncompliance include financial constraints, lack of awareness, and fear of side effects. Therefore, improving patient education and providing financial support may improve patient compliance and ultimately improve the outcomes of ROCM management.

CONCLUSIONS

Our study highlights the importance of early detection and treatment of ROCM in COVID-19 and diabetic patients The study also emphasizes the need to address the financial burden of the procedure and improve patient compliance with treatment. Further research is required to determine the long-term outcomes of ROCM in COVID-19 patients and to identify effective management strategies to reduce morbidity and mortality. It also warrants the need for local drug testing and trials of the effectiveness of locally manufactured antifungal drugs. Overall, the research offers insightful data on the gray areas of ROCM management, which may aid healthcare professionals in improving the quality of care for patients with this condition.

Future recommendation

It was observed that early detection of mucormycosis with endoscopic clearance and early administration of liposomal amphotericin B resulted in less morbidity, early recovery, fewer complications, and less hospital stay. Based on the findings, we recommend the need of development of molecular techniques for early diagnosis of mucormycosis, antifungal drugs need local manufacturing, efficacy testing & local trials are needed, offering prophylactic antifungals in very high-risk groups need clinical trials. Furthermore, and even more importantly, awareness of this deadly disease among general population and physicians is required along with rehabilitation programs

AUTHORS' CONTRIBUTION

ES: Literature search. SL, ZUSQ: Conceptualization of study. ES, ZK: Data collection. SAM: Data analysis, data interpretation. ES, IU: Proof reading.

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