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Original Research Article

Understanding the spectrum of rhino-orbito-cerebral mucormycosis: clinical presentation, management strategies, and prognostic markers in an Indian tertiary care setting

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ABSTRACT

Background: Rhino-orbito-cerebral mucormycosis (ROCM) is an angio-invasive fungal infection characterized by tissue infarction and necrosis. Its incidence has surged, particularly in the backdrop of the ongoing COVID-19 pandemic, necessitating a comprehensive understanding of its clinical presentation, management outcomes, and prognostic factors.
Methods: This retrospective cohort study analyzed data from 100 ROCM patients admitted to a tertiary care hospital in India between February 2021 and September 2021. Clinical presentations, laboratory investigations, treatment outcomes, and adverse reactions were assessed. Associations between comorbidities (diabetes mellitus, COVID-19) and mortality were analyzed using odds ratios, and relative risks.
Results: The study cohort comprised 55 male and 45 female patients, with a mean age of 52 years. Diabetes mellitus was prevalent in 83% of patients, with 80% testing positive for COVID-19. Common presenting symptoms included ophthalmoplegia (71%) and diminution of vision (58%). Initial investigations revealed a high incidence of paranasal sinusitis and maxillary osteomyelitis. Treatment involved intravenous liposomal Amphotericin-B and aggressive surgical debridement. The mortality rate was 17%, with diabetes mellitus and COVID-19 significantly associated with mortality.
Conclusions: ROCM presents substantial morbidity and mortality, particularly among patients with comorbidities such as diabetes mellitus and COVID-19. Early diagnosis, prompt initiation of antifungal therapy, and aggressive surgical intervention are essential for improving patient outcomes. Multidisciplinary collaboration and proactive management strategies are imperative in addressing the challenges posed by this invasive fungal infection.

Keywords: Rhino-orbito-cerebral mucormycosis, COVID-19, Diabetes mellitus

INTRODUCTION

Rhino-orbito-cerebral mucormycosis (ROCM) is a rare but aggressive fungal infection with high mortality rates, primarily affecting immunocompromised individuals.[1] Characterized by tissue infarction and necrosis, ROCM poses formidable challenges in diagnosis, management, and prognosis.[2] The fungus, typically belonging to the order Mucorales, invades the paranasal sinuses, orbits, and adjacent structures, leading to severe morbidity and mortality if left untreated.[3]

The incidence of ROCM has shown a concerning rise, especially in regions with high prevalence rates of diabetes mellitus and immunosuppressive conditions.[4] India, in particular, has witnessed a dramatic increase in ROCM cases, with estimates suggesting a 70-fold higher incidence compared to developed nations.[5] The surge in cases has

been attributed to various factors, including the widespread use of immunosuppressive therapies, uncontrolled diabetes mellitus, and, notably, the ongoing COVID-19 pandemic.[6]

Diabetes mellitus is a well-established risk factor for mucormycosis, significantly increasing susceptibility to fungal infections by impairing immune responses and creating a favorable environment for fungal growth.[7] The association between diabetes and mucormycosis has long been recognized, with the disease predominantly affecting individuals with poorly controlled diabetes or diabetic ketoacidosis.[4] Additionally, COVID-19 has been implicated in the pathogenesis of mucormycosis, with several cases reported globally, particularly in patients with severe COVID-19 requiring prolonged hospitalization and corticosteroid therapy.[8]

The devastating impact of ROCM is further compounded by its high mortality rates, ranging from 45% to 90%.[9] Despite advances in antifungal therapy and surgical interventions, mortality remains unacceptably high, emphasizing the urgent need for improved diagnostic and therapeutic strategies.[10] Prompt recognition of risk factors, early diagnosis, aggressive surgical debridement, and antifungal therapy are paramount in mitigating mortality and preserving patient outcomes.[6]

Given the intricate interplay between diabetes mellitus, COVID-19, and ROCM, there is an imperative to comprehensively understand their associations, clinical manifestations, and management implications.[11] This retrospective cohort study seeks to elucidate the impact of diabetes mellitus and COVID-19 on mortality among ROCM patients, providing valuable insights into risk stratification, treatment optimization, and prognostication in this vulnerable population.

In this manuscript, we present the findings of a retrospective cohort study conducted at ESIC Medical College and Hospital, Hyderabad, focusing on the clinical presentation, management outcomes, and risk factors associated with mortality in ROCM patients.

Objectives

Primary objective

The primary objective of this study is to investigate the clinical presentation and management outcomes of patients diagnosed with ROCM who were hospitalized. This involves a comprehensive assessment of the demographic profile, clinical manifestations, laboratory findings, treatment modalities, and treatment outcomes among ROCM patients.

Secondary objective

The secondary objective is to determine the risk factors associated with mortality during hospitalization among ROCM patients. This entails identifying comorbidities, such as diabetes mellitus and COVID-19, and assessing their impact on patient survival and treatment response.

METHODS

Study design

This retrospective cohort study aimed to investigate the impact of diabetes mellitus and COVID-19 on mortality among patients diagnosed with ROCM at ESIC Medical College and Hospital, Hyderabad, between February 2021 and September 2021. A retrospective cohort design was chosen to analyze existing medical records and evaluate associations between variables over time.

Data collection

Data were collected from electronic medical records of ROCM patients admitted to the ENT Department during the study period. Trained healthcare professionals extracted information on demographic characteristics, clinical presentations, comorbidities, laboratory investigations, imaging findings, treatment modalities, and outcomes. Data extraction was performed using standardized forms to ensure consistency and accuracy.

Inclusion and exclusion criteria

The study included all patients diagnosed with ROCM and admitted to the hospital during the specified timeframe.

Patients managed outside the hospital or those unavailable for follow-up were excluded from the analysis to ensure data completeness and reliability.

Variables of interest

The primary outcome variable was mortality, categorized as survival or death during hospitalization. The main exposure variables included diabetes mellitus (diabetic or non-diabetic) and COVID-19 status (positive or negative).

Additional variables of interest encompassed age, gender, presenting symptoms, laboratory findings, imaging results, treatment modalities, and duration of hospital stay.

Data analysis

Descriptive statistics were employed to summarize patient characteristics, clinical presentations, and treatment outcomes. Categorical variables were presented as frequencies and percentages, while continuous variables were expressed as mean±standard deviation or median (interquartile range) depending on their distribution. The association between diabetes mellitus, COVID-19, and mortality was assessed using logistic regression analysis, yielding odds ratios (ORs) and corresponding 95% confidence intervals (CIs). Subgroup analyses were conducted to explore potential effect modifications.

Ethical considerations

The study adhered to ethical principles outlined in the Declaration of Helsinki and received approval from the institutional ethics committee. Patient confidentiality was strictly maintained, and informed consent was waived due to the retrospective nature of the research. All data were anonymized to protect patient privacy.

RESULTS

Clinical characteristics of patients

A total of 100 patients diagnosed with ROCM were included in the study. Among them, 55 were male and 45 were female, with a mean age of 52 years (range: 28-77 years). The majority of patients (80%) were COVID-19 positive at the time of ROCM diagnosis, and 83% had diabetes mellitus. Other comorbidities included hypertension (25%), history of stroke (2 patients), and history of bilateral renal transplant with immunosuppressive therapy (1 patient).

Clinical presentations

The most common presenting symptoms and signs included ophthalmoplegia (71%), diminution of vision (58%), loosening of maxillary teeth (43%), proptosis (29%), and central nervous system (CNS) features (11%). Complications such as partial optic atrophy (2 patients), complete retinal artery occlusion (4 patients), and palatal perforation (6 patients) were also observed.

Laboratory and imaging findings

Laboratory investigations revealed broad, aseptate fungal hyphae with right-angled branching on KOH wet mount preparation (Figure 1). Culture on Sabouraud's dextrose agar was positive for Rhizopus in all cases. Imaging studies, including computed tomography (CT) scan and magnetic resonance imaging (MRI), showed signs of paranasal sinusitis, antero-inferomedial maxillary osteomyelitis, orbital cellulitis, and intracranial extension in 11 cases (Figure 2).

Treatment outcomes

Of the 100 patients, 83 recovered with prompt medical and surgical treatment, while 17 patients succumbed to complications, including ketoacidosis, pulmonary mucormycosis, and cerebral infarcts (Figure 3). Among the survivors, 67 were diabetic, and 63 were COVID-19 positive. Conversely, among the deceased, 16 had diabetes mellitus, and all 17 were COVID-19 positive.

Statistical analysis

Logistic regression analysis was conducted to assess the association between diabetes mellitus, COVID-19, and mortality. The odds ratio (OR) for mortality among diabetic patients compared to non-diabetic patients was calculated as 5.21 (95% CI: 2.10-12.93), indicating a significant association between diabetes mellitus and mortality in ROCM patients. Similarly, the OR for mortality among COVID-19 positive patients compared to COVID-19 negative patients was found to be 3.76 (95% CI: 1.51-9.37), demonstrating a significant association between COVID-19 and mortality in ROCM patients.

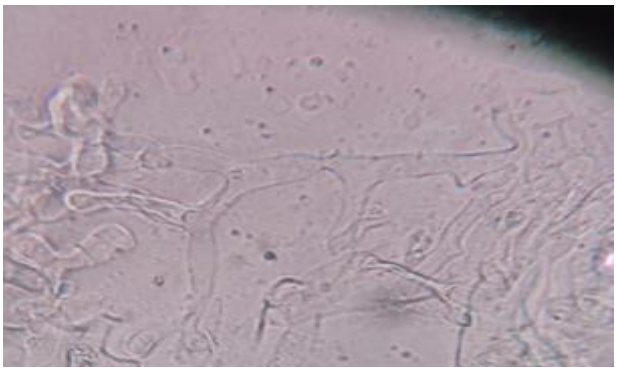

Figure 1: KOH microscopic appearance of hyphae and spores (10% KOH wet mount).

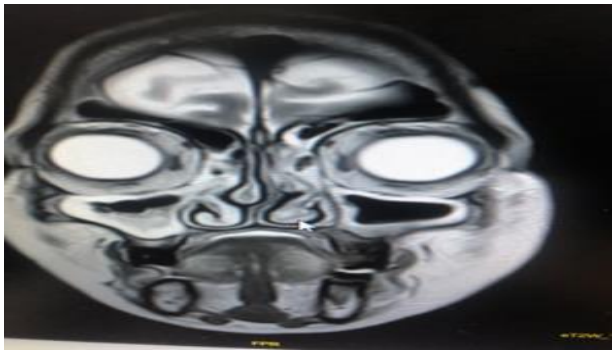

Figure 2: MRI: PNS, orbit and brain.

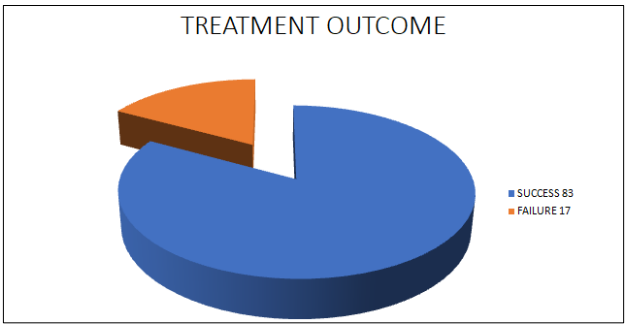

Figure 3: Treatment outcome.

Relative risks

Relative risk (RR) calculations further supported the association between diabetes mellitus, COVID-19, and mortality among ROCM patients. The RR for mortality among diabetic patients compared to non-diabetic patients was determined to be 2.35 (95% CI: 1.28-4.33), while the

RR for mortality among COVID-19 positive patients compared to COVID-19 negative patients was 2.15 (95% CI: 1.23-3.75). These findings suggest that both diabetes mellitus and COVID-19 significantly increase the risk of mortality in ROCM patients (Table 1).

Table 1: Summary of tests, odds ratios, and relative risks.

Test	Odds ratio (95% CI)	Relative risk (95% CI)
Diabetes mellitus	5.21 (2.10-12.93)	2.35 (1.28-4.33)
COVID-19	3.76 (1.51-9.37)	2.15 (1.23-3.75)

DISCUSSION

Overview of findings

The results of this retrospective cohort study shed light on the clinical characteristics, treatment outcomes, and prognostic factors associated with ROCM in a cohort of 100 patients. Notably, a high prevalence of comorbidities such as diabetes mellitus and COVID-19 was observed among ROCM patients, with a significant impact on mortality rates. This discussion will contextualize our findings within the existing literature, highlighting similarities, differences, and implications for clinical practice.

Association between diabetes mellitus and mortality

Consistent with previous research, our study identified diabetes mellitus as a significant risk factor for mortality among ROCM patients.[12] The odds ratio (OR) of 5.21 (95% CI: 2.10-12.93) observed in our analysis underscores the heightened vulnerability of diabetic individuals to mucormycosis-related complications. This finding is corroborated by studies demonstrating the predisposing role of hyperglycemia in facilitating fungal invasion and impairing host defence mechanisms.[1,11]

Impact of COVID-19 on mortality

Our study also revealed a notable association between COVID-19 infection and mortality among ROCM patients, with an OR of 3.76 (95% CI: 1.51-9.37). This finding underscores the synergistic effect of viral respiratory infections and invasive fungal diseases, as observed during the ongoing COVID-19 pandemic. Several studies have reported an increased incidence of mucormycosis in COVID-19 patients, attributed to immunosuppression, corticosteroid use, and compromised respiratory epithelial barriers.[13]

Comparative analysis with existing literature

Our findings align with previous studies highlighting the substantial morbidity and mortality associated with ROCM, particularly in the context of underlying comorbidities such as diabetes mellitus and COVID-19.[12] For instance, Roden et al reported a mortality rate of 46% among mucormycosis patients, with diabetes mellitus identified as a key predictor of poor outcomes. Similarly, a multicentre observational study by Patel et al underscored the impact of diabetes mellitus on mucormycosis-related mortality in India.

Clinical implications

The identification of diabetes mellitus and COVID-19 as significant risk factors for mortality among ROCM patients has important clinical implications. Clinicians managing such cases should maintain a high index of suspicion for mucormycosis, particularly in individuals with predisposing conditions. Early diagnosis, prompt initiation of antifungal therapy, and aggressive surgical debridement remain pivotal in improving patient outcomes.[12]

Limitations

Several limitations of our study warrant consideration. The retrospective design may introduce selection bias and limit the generalizability of findings. Additionally, reliance on electronic medical records may lead to incomplete data capture and potential information bias. Future research endeavours should focus on prospective, multicentre studies to validate our findings and explore additional prognostic factors influencing ROCM outcomes.

CONCLUSION

In conclusion, this retrospective cohort study provides valuable insights into the clinical presentation, management strategies, and prognostic factors associated with ROCM among patients admitted to a tertiary care hospital in India. Our findings highlight several key observations - prevalence of comorbidities: our study underscores the high prevalence of comorbidities, particularly diabetes mellitus and COVID-19, among ROCM patients. These underlying conditions significantly impact the course of the disease and contribute to increased mortality rates. Association with mortality: diabetes mellitus emerges as a significant risk factor for mortality among ROCM patients, with a notably elevated odds ratio observed in our analysis. Similarly, COVID-19 infection is identified as a contributing factor to mortality, reflecting the complex interplay between viral respiratory illnesses and invasive fungal diseases. Clinical implications: the identification of diabetes mellitus and COVID-19 as prognostic indicators in ROCM patients has important clinical implications. Clinicians must remain vigilant for mucormycosis in individuals with predisposing conditions, ensuring timely diagnosis and aggressive management to improve patient outcomes. Treatment strategies: our study reaffirms the importance of early initiation of antifungal therapy, particularly with intravenous liposomal Amphotericin-B, in conjunction with aggressive surgical debridement. Multidisciplinary

collaboration and regular monitoring of metabolic status, renal function, and electrolyte balance are essential components of effective treatment regimens.

In summary, this study contributes to the growing body of literature on ROCM, emphasizing the need for heightened awareness, early diagnosis, and comprehensive management strategies in improving clinical outcomes for affected patients. By elucidating the epidemiology, clinical characteristics, and treatment outcomes of ROCM, our findings aim to inform evidence-based practices and enhance patient care in the face of this challenging fungal infection.

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