



Original Article

Rhinocerebral Mucormycosis During the COVID Era: A Case Series in A Tertiary Care Centre

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ABSTRACT

Aims Rhinocerebral Mucormycosis is a rare and potentially life-threatening disease caused by filamentous fungi of the Mucorales order and Zygomycetes class. These opportunistic pathogens exhibit rapid and aggressive growth in individuals who are immunocompromised, resulting in a life-threatening condition. The present study aimed to evaluate the myriad presentations of invasive fungal sinusitis with intracranial involvement during the COVID-19 era.

Materials and Methods This study was conducted as a retrospective case series of all patients diagnosed with mucormycosis who attended the department of ENT of a tertiary care center. Case files from the medical records department of patients who were diagnosed with rhinocerebral mucormycosis were retrieved between April 2021 to October 2021.

Results A total of 24 study participants were included in this case series. Among the study participants, 75% (n=18) had nasal complaints. Unilateral and bilateral paranasal sinus involvement were reported in 25% (n=6) and 62.5% (n=15), respectively. Intracranial complications observed in the study included cerebritis (50%, n=12), cerebral infarct (29.2%, n=7), Cavernous sinus thrombosis/ invasion (16.7%, n=4), temporal lobe abscess (16.7%, n=4), frontal lobe abscess (12.5%, n=3), frontal bone osteomyelitis (8.3%, n=2), ischemic changes (4.2%, n=1), skull base osteomyelitis (4.2%, n=1). Functional endoscopic sinus surgery (FESS)/Paranasal sinus debridement was done in 62.5% (n=15) of the study participants.

Conclusion: Mucormycosis with intracranial extension poses a grave prognosis and requires high clinical suspicion. Prompt suspicion of diagnosis through neuroimaging, with timely antifungal therapy and surgical debridement, is crucial for improving outcomes.

Keywords: Rhinocerebral Mucormycosis, COVID-19, Functional endoscopic sinus surgery, Paranasal sinus debridement

INTRODUCTION

A complex interplay of factors that include diabetes mellitus, any previous respiratory pathology, immunosuppressive therapy, nosocomial infection sources and systemic immune alterations of Covid-19 infection itself may lead to secondary infection, which are increasingly being recognized in view of their impact on morbidity and mortality [1].

Mucormycosis is characterized by the presence of hyphal invasion of sinus tissue. It can develop within a period of 4 weeks. It is a life-threatening invasive fungal infection occurring in the sinusitis [1]. Rhinocerebral Mucormycosis is a rare and potentially life-threatening disease caused by filamentous fungi of the Mucorales order and Zygomycetes class [2]. It is also known as zygomycosis. They are often found in soil and decaying organic matter [3]. These are opportunistic pathogens that show a rapid and aggressive growth in individuals who are immunocompromised, hence leading to a life-threatening condition. Often, this disease requires immediate medical attention [2]. Uncontrolled diabetes, individuals who are on chemotherapy and who have chronic illness (acquired immunodeficiency syndrome, prolonged neutropenia, certain

cancers and recent organ transplants) are also at higher risk of developing Mucormycosis [3]. The affected individuals can develop other complications in the pulmonary, rhinocerebral, cutaneous and gastrointestinal systems. Among these, Rhinocerebral Mucormycosis is the most common form [4].

The sudden rise in Mucormycosis was reported during the second wave of the COVID-19 pandemic in India. The disease was also reported to be more prevalent among COVID-19 and post-COVID-19 patients [5, 6].

Mucormycosis can be confirmed using histopathological examination [4]. Management of Mucormycosis is still a big challenge and is based on different strategies which envisage a rapid diagnosis, removal or reduction of risk factors like diabetes, renal disease, rapid use of immunosuppressants and aggressive antifungal treatment with or without surgical debridement [7]. The Mortality ranges from 50-93% secondary to intraorbital and intracranial complications [8-12].

The myriad presentations of intracranial involvement in patients with Mucormycosis need to be studied in detail. Detection of the early presentation of the disease will help the ENT surgeons to combat the morbidity and mortality associated with it. Hence, this study was undertaken to explore the diverse clinical presentations of Rhinocerebral Mucormycosis among individuals with COVID-19 infection, and to ensure timely diagnosis and prompt treatment to improve patient outcomes.

The main aim of the study was to evaluate the myriad presentations of invasive fungal sinusitis with intracranial involvement during the COVID-19 era.

The objectives of the study were to assess the associated factors, duration of disease, diagnosis, and management of rhinocerebral mucormycosis during the COVID-19 era.

METHODOLOGY

The retrospective case series analysis of all patients confirmed with a diagnosis of mucormycosis who attended the Department of ENT of a tertiary care center was included in the study. The case files from the Medical Records Department of patients who were diagnosed with rhinocerebral mucormycosis were retrieved between April 2021 to October 2021.

Inclusion criteria:

- Patients with radiological evidence and histopathological confirmation of mucormycosis with intracranial extension, attending the Department of ENT of a tertiary care center, were included in the study during the COVID period.
- Patients who are 18 years or above.

Exclusion criteria

- RTPCR positive Mucormycosis during admission and COVID-19, with a patient who were highly oxygen dependent.
- Patients who had undergone surgery at other hospitals or health institutes.

Statistical Analysis

The data collected was entered into a Microsoft Excel sheet and was analyzed using IBM SPSS version 27.0. Data was presented using descriptive statistics. Continuous data was represented as mean and standard deviation; categorical data was represented as frequency and percentage.

RESULTS

Age and Gender

A total of 24 study participants confirmed diagnosis as mucormycosis by histopathological evaluation were included in this case series. The mean age of the study participants was 47.66 ± 11.14 years. The majority of the study participants were males (Male: n=20, 83.3%, Female: n=4, 16.7%) (Table 1).

Table 1: Demographic details and comorbidities of study participants

Variables	Patients (n (%))
Mean Age	47.66 $\pm$ 11.14
Gender	
Male	20 (83.3%)
Female	4 (16.7%)
Comorbidities	
Diabetes	23 (95.8%)
Hypertension	2 (8.3%)

Cardiovascular disease	2 (8.3%)
Hypothyroidism	2 (8.3%)

Comorbidities:

Among the study participants, 95.8% (n=23) had diabetes, with 16.6% (n=4) newly diagnosed and 16.6% (n=4) had diabetic ketoacidosis. Hypertension, cardiac diseases and hypothyroidism were present in 8.3% (n=2) each. None of the study participants were vaccinated for COVID-19 infection.

Presenting complaints

Among the study participants, 75% (n=18) had nasal complaints. Nasal discharge and nasal obstruction were reported in 16.7% (n=4) and 12.5% (n=3) of the study participants respectively, with 45.8% (n=11) of the participants presenting with both symptoms.

Loss of vision, blurring of vision, orbital pain, swelling of the eye and ptosis were present in 33.3% (n=8), 29.2% (n=7), 16.7% (n=4), 33.3% (n=8) and 12.5% (n=3) respectively.

Facial swelling, headache and toothache were present in 33.3% (n=8), 66.7% (n=16) and 8.3% (n=2) respectively.

Examination

The Glasgow Coma Scale (GCS) was 15 for all the patients except one patient, with a value of 10 for 15. On examination, one patient was drowsy and disoriented.

Black necrotic eschar was present in the nasal cavity of 12.5% (n=3) and yellow crusts were present in the nasal cavity of 20.8% (n=5) of the study participants. Palate erosion was reported in 4.2% (n=1) of the study participants (Table 2).

Table 2: Presenting complaints and examination of study participants

Variables	Patients (n (%))
Nasal Complaints	
Both nasal discharge and obstruction	18 (75%)
Only nasal discharge	4 (16.7%)
Only nasal obstruction	3 (12.5%)
Visual/ Orbit Complaints:	
Loss of vision	8 (33.3%)
Swelling of eye	8 (33.3%)
Blurring of vision	7 (29.2%)
Orbital pain	4 (16.7%)
Ptosis	3 (12.5%)
Central nervous system:	
Headache	16 (66.7%)
Altered sensorium	1 (4.2%)
On Examination:	
Black necrotic eschar in nasal cavity	3 (12.5%)
Yellowish crusts in nasal cavity	5 (20.8%)
Palate erosion	1 (4.2%)

Investigations

The mean total leukocyte count (TLC) of the study participants was 9056.52 ± 3220.36 cells/ μ L. Mean C-reactive protein (CRP) among the study participants was 59.11 ± 81.87 mg/L. The mean random blood sugar (RBS) among the study participants was 141.43 ± 61.57 mg/dL. Mean HbA1c values of the study participants were $8.75 \pm 1.34\%$. Urine ketone bodies (UKB) were present in 2 (8.3%) study participants. The KOH test was positive in one patient. 24 study participants (100%) had a histopathological report confirming Mucormycosis. (Table 3).

Table 3: Biochemical investigations of study participants

Biochemical Investigations	Mean Value
TLC (cells/ μ L)	9056.52 ± 3220.36
CRP (mg/L)	59.11 ± 81.87
RBS (mg/dL)	141.43 ± 61.57

HbA1c (%)	8.75 ± 1.34
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Radiological findings

The majority of the study participants had maxillary and ethmoid sinus involvement (n=20, 83.3% each), followed by sphenoid (n=15, 62.5%) and frontal (n=7, 29.2%). Unilateral and bilateral paranasal sinus involvement were reported in 25% (n=6) and 62.5% (n=15) respectively.

Unilateral and bilateral orbital involvement were reported in 20.8% (n=5) and 12.5% (n=3) respectively.

Cerebritis was the predominant CNS involvement reported among the study participants (n=12, 50%), followed by infarct in 29.2% (n=7), cavernous sinus thrombosis/ invasion in 16.7% (n=4), temporal lobe abscess in 16.7% (n=4), frontal lobe abscess in 12.5% (n=3), skull base osteomyelitis in 8.3% (n=2), ischemic changes in 4.2% (n=1) and frontal bone osteomyelitis in 4.2% (n=1) (Table 4) (Figure 1, 2 and 3).

Table 4: Radiological findings

Findings	Patients (n (%))
Laterality of paranasal sinus involvement	
Bilateral	15 (62.5%)
Unilateral	6 (25%)
No involvement	3 (12.5%)
Predominant paranasal sinus involvement	
Maxilla	20 (83.3%)
Ethmoid	20 (83.3%)
Sphenoid	15 (62.5%)
Frontal	7 (29.2%)
Orbital involvement	
No involvement	16 (66.7%)
Unilateral	5 (20.8%)
Bilateral	3 (12.5%)
Laterality of CNS involvement	
Bilateral	17 (70.8%)
Unilateral	7 (29.2%)
Predominant CNS involvement	
Cerebritis	12 (50%)
Infarct	7 (29.2%)
Cavernous sinus thrombosis/ invasion	4 (16.7%)
Temporal lobe abscess	4 (16.7%)
Frontal lobe abscess	3 (12.5%)
Frontal bone osteomyelitis	2 (8.3%)
Ischemic changes	1 (4.2%)
Skull base osteomyelitis	1 (4.2%)

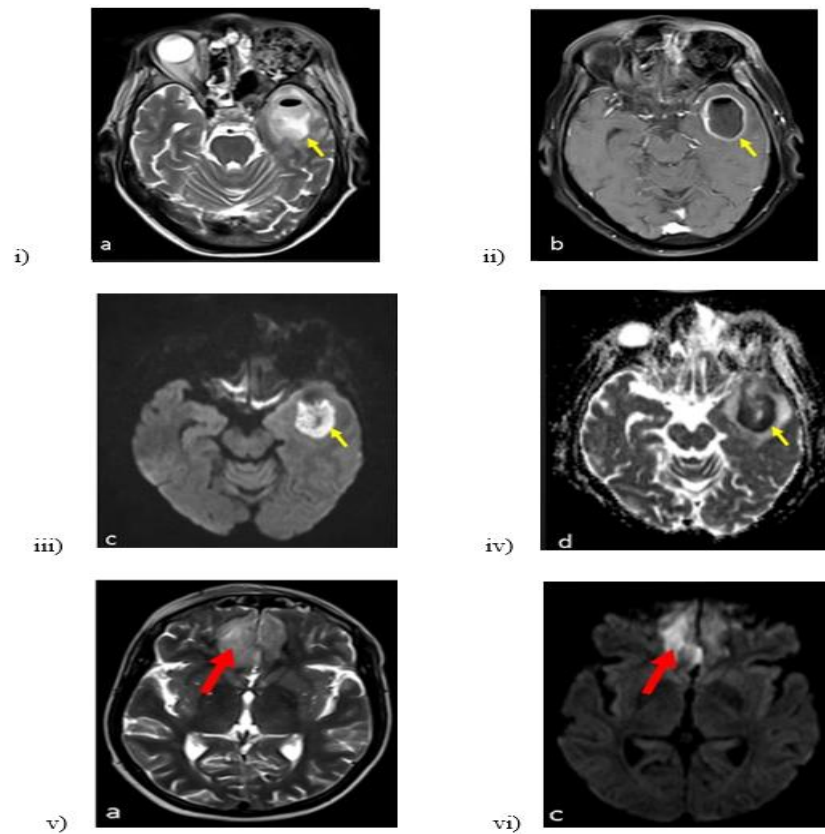


Figure 1: i) to iv) Temporal lobe abscess; v) and vi) Rhinocerebral mucormycosis with frontal lobe involvement

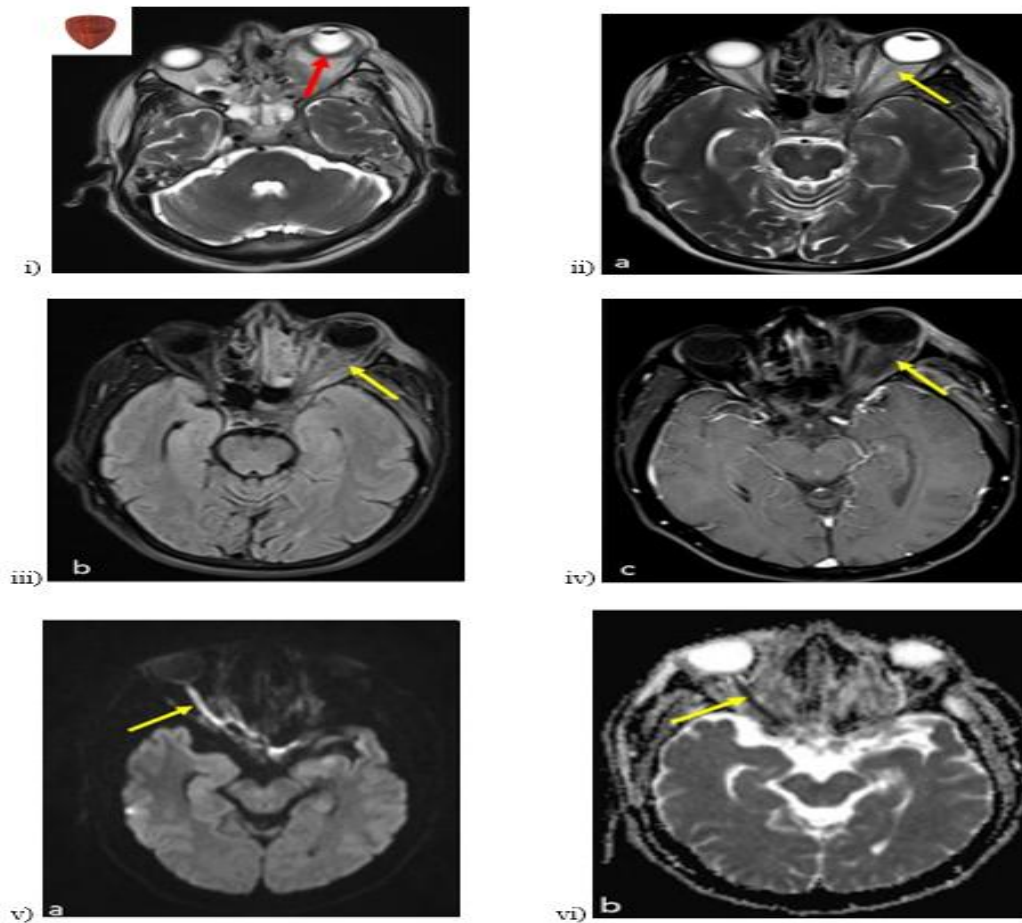


Figure 2: i) Guitar pick sign; ii) to iv) Rhino-orbital mucormycosis with retro orbital involvement; v) and vi) Ischemic optic neuropathy

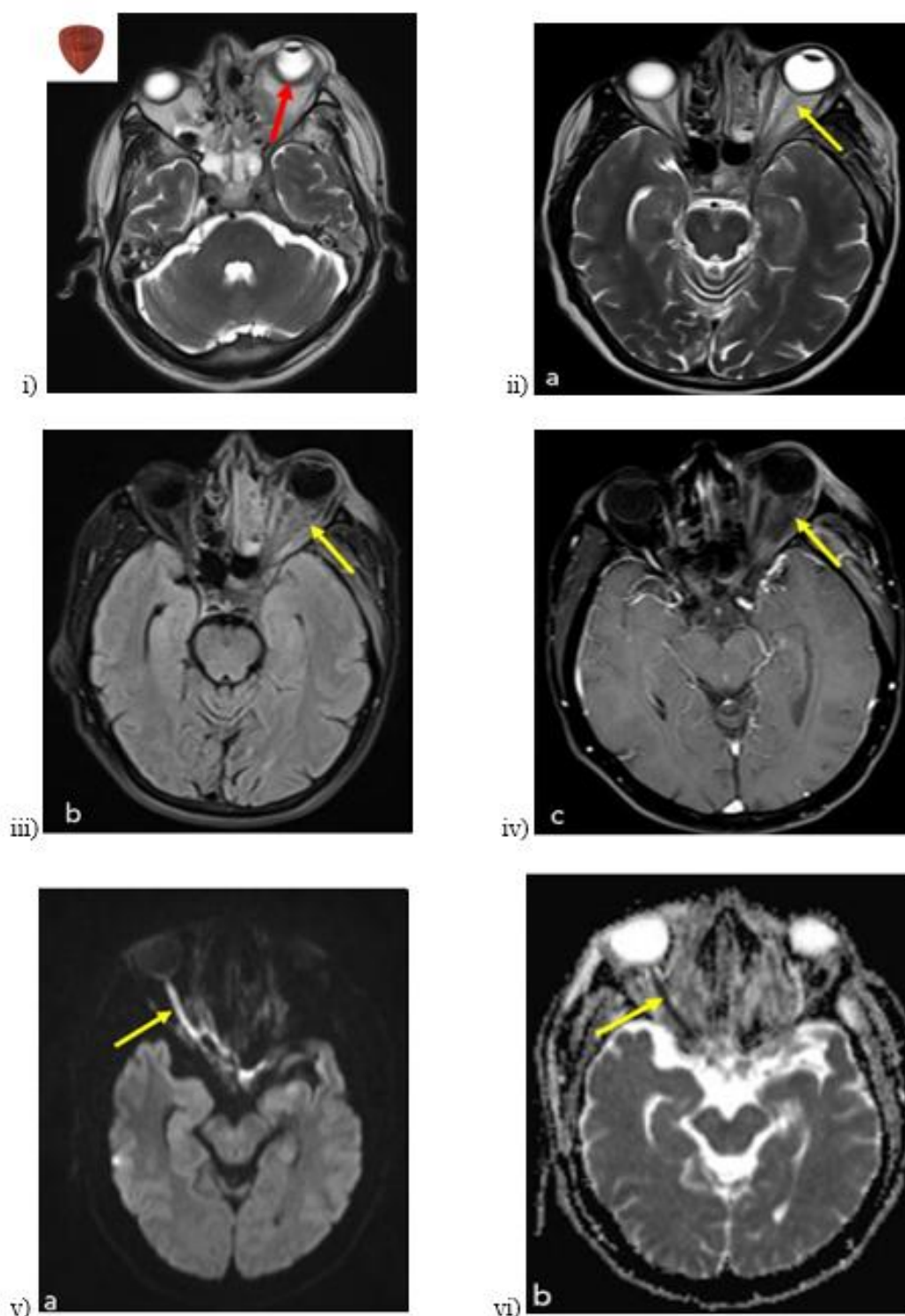


Figure 3: i) Sino nasal mucormycosis; ii) to iv) Sino nasal mucormycosis with masticatory and infra temporal fossa involvement; v) and vi) Internal carotid artery thrombosis vii) and viii) Skull base involvement

Management

Surgical management

Paranasal sinus debridement/functional endoscopic sinus surgery (FESS) were done in 62.5% (n=15) of the study participants. Paranasal sinusitis debridement/ FESS and orbital exenteration were done in 5 individuals (20.8%). Four study participants (16.6%) were not fit for the surgery.

Medical management

Inj. Liposomal Amphotericin B (AMP B) was given to 70.8% (n=17) of the study participants with different doses and Tab. Posaconazole for one study participant n=1 (4.2%).

Combination therapy of oral drugs and intravenous drugs were given for 25% (n=6) of the study participants with combination of Inj. Liposomal Amphotericin Band Tab. Posaconazole with various compositions (Table 5).

Table 5 : Management

Treatment	Patients (n (%))
Aggressive surgical debridement	
Paranasal sinusitis debridement / FESS	15 (62.5%)
Paranasal sinusitis debridement / FESS + Orbital exenteration	5 (20.8%)
Combination therapy (IV and oral)	
Inj. Liposomal AMP B (Less than 1g) and Tab. Posaconazole 300 mg (2.7gm-4.5gm)	4 (16.7%)
Inj. Liposomal AMP B (1.9g) and Tab. Posaconazole 300 mg (4.8gm)	1 (4.2%)
Inj. Liposomal AMP B (2.5g) and Tab. Posaconazole 300 mg (3gm)	1 (4.2%)
Mono Therapy	
Inj. Liposomal AMP B Less than 1g	8 (33.3%)
Inj. Liposomal AMP B 1-2g	2 (8.3%)
Inj. Liposomal AMP B 2.6g	1 (4.2%)
Inj. Liposomal AMP B 3-4g	2 (8.3%)
Inj. Liposomal AMP B 4-5g	4 (16.7%)
Tab. Posaconazole 300mg (1.2gm)	1 (4.2%)

Outcome

Among the study participants, 16.7% (n=4) expired and 83.3% (n=20) were discharged after treatment (Table 6).

Table 6: Outcomes of study participants

Outcome	Patient (n (%))
Discharged	20 (83.3%)
Death	4 (16.7%)

Table 7: Death Summary

S No.	Cause of Death	Radiological Finding (MRI)
1.	Cardiorespiratory arrest with rhino-orbito-cerebral mucormycosis with acute CVA with right sided hemiparesis	Right Cerebrovascular infarct
2.	Cardiorespiratory arrest with uncal herniation secondary to rhinoorbitocerebral mucormycosis with right temporal abscess.	Right Temporal lobe abscess.
3.	Sepsis with septic shock with cavernous sinus thrombosis with rhinoorbitocerebral mucormycosis with bronchopneumonia	Right Cavernous sinus thrombosis
4.	Thromboembolism and fungemia with left rhinoorbitocerebral mucormycosis.	Skull base osteomyelitis

DISCUSSION

Mucormycosis or zygomycosis, also called phycomycosis, initially described in 1885 by Paltauf, is an uncommon and aggressive fungal infection that usually affects patients with alterations of their immunological system. Rhinocerebral Mucormycosis is its most common form. Rhizopus, Mucor, and Absidia species are the commonest causative organisms [1].

The mean age of the study participants in the present case series was 47.66 ± 11.14 years. A lower mean age of 37 ± 12.52 years was reported in a study conducted by Sahni et al., in Punjab, showing an increase in the incidence of Rhinocerebral Mucormycosis post-COVID-19 era [5]. A higher mean age of 51.9 years was reported in the OPAI-IJO study on Mucormycosis in COVID-19 (COSMIC) study group [6]. A similar high mean age of 58.2 years was reported in a ten-year single-center case series conducted in Iraq by Balai E et al [7]. The age of the study participant in the El Korbi et al. study was 62 years male [16].

In the present study, the majority of the study participants were males (Male: n=20, 83.3%, Female: n=4, 16.7%). Similar results were reported in other studies [5, 6, and 7].

In the present study, almost all the patients had diabetes (n=23, 95.8%), with 16.6% (n=4) newly diagnosed and 16.6% (n=4) had diabetic ketoacidosis. The prevalence of hypertension, cardiovascular disease and hypothyroidism was 8.3% (n=2) each respectively, in the current study. In the Sahni et al. study, all the study participants had diabetes. Both diabetes and hypertension were present in 39.58% (n=19) of the study participants. Renal diseases were present in 7.2% (n=7) of the study participants [5]. Similarly, in the Balai E et al. study, all the study participants had diabetes [7]. In the COSMIC study group study, 80% (n=690) of the study participants had hypertension, 78% (n=2194) of the study participants had diabetes, 10% (n=88) had renal diseases, 1.9% (n=16) had cardiovascular diseases, and 0.5% (n=4) had thyroid disorders. In the review paper published by Kumar M et al., with 219 study participants with Rhinocerebral Mucormycosis, 57.4% (n=126) had diabetes [15]. The study participants of El Korbi et al. had diabetes [16]. A single-case study conducted by Mehta S showed that the study participant had diabetes [19]. The majority of the study participants in the case series conducted by Sharma et al. had diabetes (n=57, 93.4%) [17]. Diabetes, especially the uncontrolled blood glucose levels (ketoacidosis), is a favorable condition for the development of the fungus. Hence, a higher prevalence of diabetes is reported in Mucormycosis. Patients with a history of COVID-19, particularly when treated with corticosteroids, have been shown to develop Mucormycosis at a higher incidence in India. The immune dysregulation due to the disease and the effects of immunosuppressants favor the environment for fungal development. Other diseases, like kidney disease and immunosuppressive conditions, were also highly susceptible to the development of Rhinocerebral Mucormycosis.

In the present study, 75% (n=18) had nasal complaints (nasal discharge, nasal obstruction), and nasal discharge and nasal obstruction were reported individually in 16.7% (n=4) and 12.5% (n=3) respectively. In the present study, 62.5% (n=15) had complaints related to the eyes. Loss of vision, blurring of vision, orbital pain, swelling of the eye and ptosis were present in 33.3% (n=8), 29.2% (n=7), 16.7% (n=4), 33.3% (n=8) and 12.5% (n=3) respectively. Facial swelling, headache and toothache were present in 33.3% (n=8), 66.7% (n=16) and 8.3% (n=2) respectively. In the Sahni et al. study, Blood-stained nasal discharge was present in all the study participants. Reduced visual acuity/ chemosis/ proptosis was present in 88.9% (n=8) of the study participants. Facial pain/ numbness/ headache was present in 34% (n=43) of the study participants [7]. A review study conducted among 49 study participants who were immunocompetent had sino-nasal mucosal involvement, followed by surrounding soft tissue and orbit [14]. In the review by Kumar M et al., maxillary involvement was commonly found in 59.2% (n=130), followed by intra-oral lesions in 34.2% (n=75) [15]. On examination, the study participant in El Korbi et al., study had frontal swelling with oedema of the upper eyelid (right)[16].

In the present study, the majority of the participants had maxillary and ethmoid sinus involvement (n=20, 83.3% each), followed by sphenoid (n=15, 62.5%) and frontal (n=7, 29.2%), whereas 12.5% (n=3) showed no paranasal sinus involvement. A similar result was reported in the study by Sahni et al., the incidence of sinus affected were ethmoid (n=46, 43.4%), maxillary (n=39, 36.8%), sphenoid (n=11, 10.4%) and frontal (n=10, 9.4%) [5]. Unilateral and bilateral involvement of paranasal sinusitis were 59% (n=1585) and 40% (n=1050) respectively, in the COSMIC study group. Paranasal sinus involvement was in maxilla (n=767, 32%), ethmoid (n=512, 21%), sphenoid (n=85, 3.5%) and frontal (n=13, 0.5%) [6]. In the nasal endoscopy of a study participant in El Korbi et al., there was the presence of pus in the middle meatus and a necrotic appearance of the middle turbinates [16]. Significant mucosal thickening was reported in the right frontal, maxillary, and ethmoid sinus in the study participant of Mehta S case study [19].

Unilateral and bilateral orbital involvement were reported in 20.8% (n=5) and 12.5% (n=3) respectively, in the present study. Unilateral and bilateral orbital involvement were present in 63% (n=1687) and 8.6% (n=230) of the study participants respectively, in the study conducted by the COSMIC study group [6].

In the present study, Cerebritis was the predominant CNS involvement reported among the study participants (n=12, 50%), followed by infarct in 29.2% (n=7), cavernous sinus thrombosis/ invasion in 16.7% (n=4), temporal lobe abscess in 16.7% (n=4), frontal lobe abscess in 12.5% (n=3), skull base osteomyelitis in 8.3% (n=2), ischemic changes in 4.2% (n=1), and

frontal bone osteomyelitis in 4.2 (n=1). Cavernous sinus thrombosis/ invasion was reported in 53% (n=285) of the study participants in COSMIC Study, followed by internal carotid artery stenosis/ occlusion in 18% (n=95), temporal lobe abscess in 12% (n=66), frontal lobe abscess in 2.8% (n=15), and skull bone osteomyelitis in 7.1% (n=38) [6]. Temporal lobe abscess (n=23, 25.7%), followed by frontal lobe abscess (n=15, 16.6%) were the commonly presented Rhinocerebral Mucormycosis [17].

In the present study, Inj Amphotericin B was given to 70.8% (n=17) of the study participants with different doses and Tab. Posaconazole was given to 4.2% (n=1) of study participants as monotherapy. Combination therapy of intravenous and oral medications was given in 25% (n=6) of the study participants with a combination of Inj. Liposomal AMP B and Tab. Posaconazole with various compositions. Combination therapy of intravenous amphotericin B and Tab. Posaconazole was given in 96% (n=633) of the study participants [6]. Oral Posaconazole was given for 95% (n=698) and oral Isavuconazole was given for 4.6% (n=34) of the study participants [6]. All the study participants were started with intravenous amphotericin B, followed by oral Posaconazole in the study conducted by Sahni et al. [5]. The majority of the study participants were managed with Amphotericin B in the review conducted by Kumar M et al. [15]. Intravenous administration of amphotericin B was provided and two months of antifungal treatment were given to the study participant in El Korbi et al., [16]. Liposomal amphotericin B was the commonly used treatment for the study participants in the Patel A et al study [18]. Cessation of steroid therapy and addition of amphotericin B was prescribed for the study participant in Mehta S case study [19].

In the present study, Paranasal sinusitis debridement or functional endoscopic sinus surgery (FESS) was done in 62.5% (n=15) of the study participants. Paranasal sinusitis debridement/ FESS and orbital exenteration were done in 5 individuals (20.8%). FESS/ paranasal sinusitis debridement was done in 67% (n=1585) of the study participants. Orbital exenteration was done in 15% (n=339) of the study participants. Both procedures were done in 17% (n=367) of the study participants [6]. 88.1% (n=52) of the study participants had undergone surgical debridement in the Sahni et al study [5]. In Kumar M et al., review, the majority of the study participants had undergone surgical debridement [15]. Surgical debridement was done for the study participant in El Korbi et al., [16].

The mortality rate in the present study was 16.7% (n=4). The mortality rate in the study conducted by Sahni et al. was 11.9% (n=7) [5]. Mortality rate in the study conducted by the COSMIC study group was 14% (n=305) [6]. A higher mortality rate of 77% (n=7) was reported in the 10-year follow-up case series study [7]. The mortality rate in the review study was 8.2 (n=4) [14]. Mortality rate in Kumar M et al., review was 18.4% (n=40) [15]. Mortality rate in the case series conducted by Sharma et al., was 42.6% (n=39) at 3-month follow-up [17]. Mortality rate among study participants in Patel A et al., study was 45.7% (n=117) at 12-week follow-up [18].

There are a few limitations in the study. The data was collected in a single center; hence, the data may not be representative in other geographical locations or settings. Once discharged, data on the follow-up of the patient could not be retrieved.

CONCLUSION

Diabetes was present among 95.8% of the study participants. Study participants confirmed with mucormycosis was treated and managed by surgical and medical management. Post-COVID mucormycosis with intracranial extension poses a grave prognosis and requires high clinical suspicion, especially in immunocompromised patients. Prompt suspicion of diagnosis through neuroimaging, coupled with timely antifungal therapy and surgical debridement, is crucial for improving outcomes.

SOURCE OF FUNDING

Nil

COMPLIANCE WITH ETHICAL STANDARDS

The authors declare no known conflicts of interest. The study involves the use of retrospectively collected data from the hospital records, personal or identifying information was kept confidential.

ETHICS APPROVAL

Institutional ethics committee approval was obtained for the retrospective study.

STATEMENT OF CONSENT

Written consent was obtained from the participants during admission for use of data for future study/academic purpose.

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