DOI: 10.5603/OJ.2023.0016

Clinical study of rhino-orbital-cerebral mucormycosis in COVID-19 patients in a regional institute in South India

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ABSTRACT

BACKGROUND: Rhino-orbital-cerebral mucormycosis (ROCM) is usually seen in immunosuppressed conditions like uncontrolled diabetes mellitus (DM). The pandemic of severe acute respiratory syndrome coronavirus 2 (Sars-CoV-2) and its associated immunosuppression and indiscriminate use of corticosteroids emerged as a new risk factor for ROCM during its' second wave of coronavirus disease 2019 (COVID-19), especially in India. The lack of standardized management protocol for ROCM needs the attention of the ophthalmic community. COVID-19-associated risk factors have been linked to the pathogenesis of ROCM, which reached epidemic proportions during India's second wave of the pandemic. The aim of the present study was to document cases of ROCM and to evaluate risk factors, including co-morbidities, clinical characteristics, diagnosis, management, and outcome at tertiary care centers during the Sars-CoV-2 (2021) pandemic.

MATERIAL AND METHODS: It is a retrospective study of 42 patients of biopsy-proven mucormycosis. These patients' records were reviewed from hospital data. All patients were subjected to complete ophthalmological, ortorhino-laringological examination, and imaging studies. The orbital staging was done. Each case was treated by a multidisciplinary approach with functional endoscopic sinus surgery (FESS) and intravenous (*i.v.*) amphotericin B (AMB). Retrobulbar liposomal AMB and exenteration were performed whenever indicated. Statistical analysis was done using the Chi square test. A p-value ≤ 0.05 was considered significant.

RESULTS: Total 42 patients of ROCM were documented. The mean age was 50.48 years, with a male preponderance (82.9%). 99.8% of patients had diabetes (39 patients) and all patients were COVID-19-positive. Concurrent steroid use was seen in 83.3% where 73.1% of patients had received oxygen support during COVID-19 infection. The most common ophthalmologic presentation was orbital/facial oedema (33) and pain, diminution of vision (24), and ophthalmoplegia (26). Direct nasal endoscopy and biopsy were done to establish a diagnosis. All patients were treated with FESS and *i.v.* AMB. Retrobulbar AMB was given to 11 patients. Exenteration was done in (n = 4) 10.5% of cases. 41 patients recovered, and one patient died

CONCLUSION: The most significant predisposing factors for developing COVID-19-associated ROCM are corticosteroids and DM. Patients with COVID-19 must be followed up even after recovery. For a favorable outcome with lower mortality in COVID-19 recovered patients, we must have a high index of clinical suspicion with awareness of red flag signs and make a timely diagnosis.

KEY WORDS: COVID-19; rhino-orbital-cerebral mucormycosis; retrobulbar amphotericin B

Ophthalmol J 2023; Vol. 8, 72–80

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INTRODUCTION

Rhino-orbital mucormycosis is an acute and often lethal opportunistic fungal infection typically affecting diabetic (50% of the cases) or immunocompromised patients caused by fungi of the class zygomycetes [1, 2]. Mucorales are rare but opportunistic pathogens and primarily affect immunocompromised people. Their invasion of blood vessels and vasculotropism leads to tissue infarction [3].

The coronavirus disease 2019 (COVID-19) infection caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may be associated with a wide range of disease patterns and altered immune system and neutropenia [4]. The increased incidence of Rhino-orbito-cerebral mucormycosis (ROCM) in the setting of COVID-19 in India and elsewhere has become a matter of concern. The full spectrum of the condition is covered under the term ROCM. With very few exceptions, it often begins in the tissues of the sino-nasal cavity (limited sino-nasal illness), moves on to the orbits (limited rhino-orbital disease), and then affects the central nervous system (ROCM disease). Patients display signs and symptoms that are related to the tissues involved.5

A hallmark of mucormycosis infection is the presence of extensive angio invasion with resultant vessel thrombosis and tissue necrosis.6 Therefore, histopathology must show evidence of tissue invasion for a diagnosis.

The most frequent course of treatment involves extensive surgical debridement of all affected tissues, including exenteration of affected orbits and prolonged administration of Amphotericin B (AMB) [7–10]. This retrospective study was carried out to evaluate risk factors, including co-morbidities, clinical characteristics, diagnosis, management and outcome.

MATERIAL AND METHOD

This is a retrospective study of patients with ROCM with a concurrent or past history of COVID-19 infection reported between April 2021 and September 2021. A total of 42 biopsy-proven Mucormycosis patients were enrolled in the study, and their hospital records were reviewed.

At the presentation, each patient was subjected to complete history taking, and otorhinolaryngologic, ophthalmic, and neurologic examinations. Detailed history and examination, including visual acuity assessment, slit-lamp evaluation, extraocular movements, and fundus examination, were done to note the presenting ophthalmic complaints and clinical characteristics. A complete history regarding Sars-Cov-2 infection with a report and systemic illness was elicited. COVID-19 reports, along with CT scores, were collected in patients who had concurrent COVID-19 with ROCM.

Table 1. Patient demographics

Demographic	Number (%)
Age [years]	
Mean age	50.48%
25–40	5
41–55	10
56–70	25
71–85	2
Sex	
Male	31
Female	11
Laterality	
OD	23
OS	17
Bilateral	02

OD (*oculus dexter*) — right eye; OS (*oculus sinister*) — left eye

The diagnosis was made on histopathological examination and KOH preparation of biopsy specimens obtained from the nasal cavity and/or paranasal sinuses. Contrast-enhanced magnetic resonance imaging (MRI) and computerised tomographic (CT) scans of the paranasal sinuses, orbits, and brain were obtained to assess the extent of the disease. Proven ROCM was defined as clinic-radiological features and microbiological confirmation on direct microscopy and/or culture. Initial investigations included complete blood counts, blood urea, serum creatinine, and serum glucose. Following this, all the patients were classified into the proposed staging system7 and managed accordingly.

Intravenous liposomal AMB was given in all the diagnosed patients under the physician's guidance in a dose of 3 to 5 mg/kg body weight/day. These patients were also treated to correct metabolic derangements on an average of 2 weeks. Functional endoscopic sinus surgery (FESS) with debridement was done by otorhinolaryngologist. The retrobulbar liposomal AMB injection was given by Ophthalmologists in cases with ocular movement restriction, ie, stage 2–3b. A minimum of 5 doses and a maximum of 7 doses through the transcutaneous retrobulbar

route were given. The dose given was 3.5mg/ml in retrobulbar space on alternate days. Reconstitution was prepared as follows: dilute a 50 mg/mL vial of liposomal amphotericin-B with 10 mL of sterile water, from that 0.7 mL is taken which contains 3.5 mg of liposomal amphotericin-B, which is further diluted to 1 mL by adding 0.3 mL of sterile water. Exenteration was considered in patients with stage 3a-c without light perception, total ophthalmoplegia, apparent necrosis of orbital tissue, and worsening despite the above concurrent systemic management.

These patients were subjected to repeat ophthalmological, ENT examination, and imaging studies to know the disease resolution or worsening. Repeat sinus and/or local tissue debridement was done on worsening. A negative sinus biopsy and normal metabolic parameters confirmed the resolution. After that, the patient was discharged with continued medical management of comorbidities. Oral Posaconazole (5 mg/kg body weight/day) was continued even after discharge for a minimum of 8 weeks as per protocol [11].

The patients were then followed up for 2 months to know the outcome.

Statistical analysis

Statistical analysis was done using Chi-square test in the Microsoft Excel program (Microsoft Corporation. Redmond, Washington, United States. Microsoft Excel [Internet]. 2018. Available from: https://office.microsoft.com/excel)

Informed consent was obtained from all the patients**.** The study was approved by the institutional Ethical Committee.

RESULTS

A total of 42 patients of COVID-19 patients associated with ROCM were analysed. The mean age noted was 50.48 (range, 28–78) years with a male preponderance (82.9%) and is tabulated below.

Figure 1 provides specifics regarding the severity of COVID-19 and its management. All patients were hospitalised for COVID-19 treatment because they all had symptoms. Of those patients, 71.4% (30) needed oxygen support. Remdesivir was administered to 83.3% (35) of them. 83.3% (35) of patients were given systemic corticosteroids orally, intravenously, or both.

Risk factors

Of the total 42 patients, 39 were diabetic, and steroid was used for treatment in 35. So, regardless of control, DM status emerged as the risk factor among all systemic co-morbidities. Acute or chronic renal failure occurred in 2% (1 patient) and hypertension in 38.09% (16 patients) of the 42 patients with other co-morbidities, respectively (Fig. 2). A total of 2% of patients who did not have diabetes mellitus (DM) or received corticosteroids got ROCM.

Clinical presentation

Out of 42 patients, 38 presented mucormycosis after 20 days to 1 month after the COVID-19 infection, and 4 presented with concurrent COVID-19 infection. Even though the most common primary symptoms of ROCM were nasal block/nasal stuffiness, the common orbital complaint seen was orbital pain and swelling. All orbital symptoms are tabulated in Table 2 — clinical presentation. Eyelid

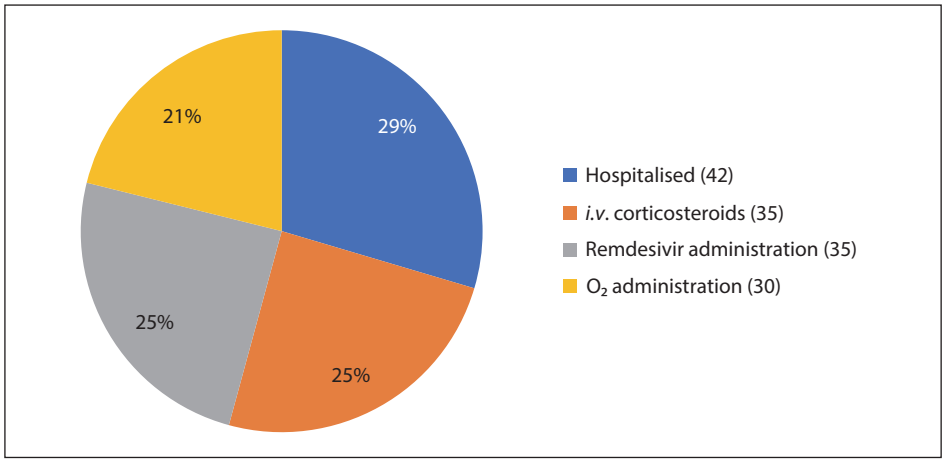

FIGURE 1. ROCM with COVID-19 management in 42 patients. *i.v.* — intravenous

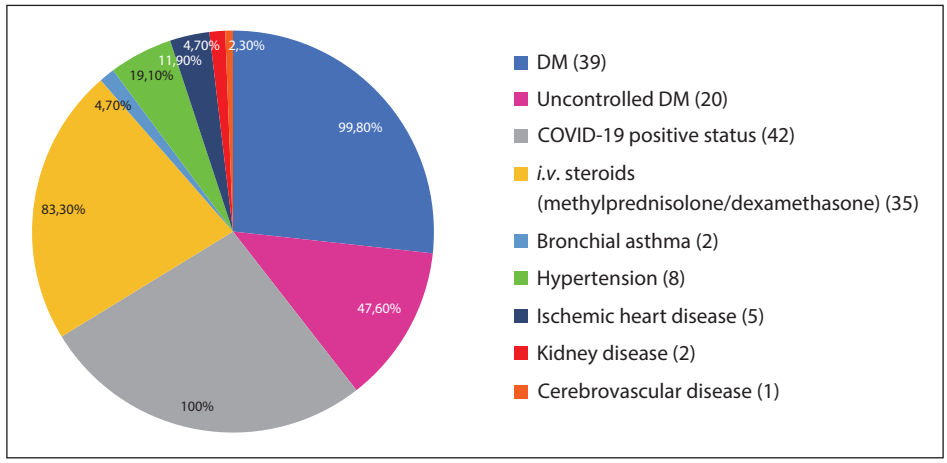

FIGURE 2. Risk factors. DM — diabetes mellitus; *i.v.* — intravenous

swelling and facial edema were the most common sign orbital signs, followed by proptosis, EOM restriction, and ptosis. The mean amount of proptosis measured was 3.1 mm.

Diagnosis and radiological findings

Diagnostic nasal endoscopy was performed for all 42 patients. Microbiological evidence was obtained in the form of direct microscopy of potassium hydroxide (KOH) preparation in 42 patients, histopathological examination in 42 patients and fungal culture in 20 patients. Figure 3 shows imaging findings. Pansinusitis followed by orbital cellulitis were the most common imaging findings noted.

Management

Management of ROCM associated with COVID-19 was a multidisciplinary approach.

Primary initiation of medical management was done in all 42 patients with *i.v.* AMB. Of 42 patients, liposomal AMB was given to 40 patients, AMB deoxycholate was given to 2, and *i.v.* AMB was given to 33 patients for a mean period of 9.1 (range, 1–60) days. AMB and Posaconazole or Isavuconazole combination therapy was given to 15 patients. 33 patients had step-down therapy with oral posaconazole or isavuconazole after stopping *i.v.* AMB.

Thirty-three patients underwent FESS/PNS debridement, of whom 10 underwent multiple sessions to clear the residual/recurrent disease. Retrobulbar AMB injection was given in 11 patients and was repeated in a range of 5–7 injections based on clinical recovery. Orbital exenteration was performed in 4 patients out of 42. Four patients (out of 42) had cerebral involvement, of whom 2 patients underwent FESS combined with exenteration, 1 patient was treated only with *i.v.* AMB plus FESS and 1 patient was intervened with FESS plus cerebral abscess drainage by neurologist. The treatment given is briefed in Table 3.

The outcome of COVID-19 associated ROCM

All patients were followed-up with oral Posaconazole as a step-down therapy. Out of 33 patients who received *i.v.* AMB and underwent FESS, 10 had recurrent disease and underwent multiple sessions of sinus debridement.

11 patients received retrobulbar AMB, and did not have further progression of orbital disease. They had a stable vision, and normal fundus, but extraocular muscle restriction remained the same. One patient developed frontal osteomyelitis during follow-up.

Four patients underwent exenteration simultaneously with FESS. Two patients were successfully treated and doing well. One patient developed recurrence and underwent repeat sinus debridement. One patient succumbed due to the spread infection and cerebral involvement. Two patients had treatment success with no recurrent disease at follow-up.

DISCUSSION

Although mucormycosis is extremely rare in healthy people, it is more common in people with immunosuppressed conditions. These conditions include uncontrolled DM with or without ketoacidosis, haematological and other cancers, or-

Table 2. Clinical characteristics	
	Number of patients
Nasal stuffiness/block	40
Redness/itching in eyes	6
Ptosis	23
Loss of vision/diminution of vision	24
Orbital/facial swelling	33
Proptosis	15
Orbital/facial pain	32
Head ache	20
Diplopia	1
Loose tooth/pain	4
Facial deviation	2
Fever	7
On examination	
Visual assessment	
6/6–6/18	16
6/18–6/60	11
< 6/60	11
PL negative	4
Ocular findings	
Frozen globe	5
EOM restriction	26
Lagophthalmos	4
Proptosis	26
Ptosis	23
Facial palsy	2
Chemosis	19
Necrosis/nasal ulcer/eschar	12
Non-reactive pupils	5
Relative afferent pupillary defect	3
CSF rhinorrhoea	1
Eyelid swelling/orbital edema/facial edema	33
Significant fundus findings	
Central retinal artery occlusion	4
Vitritis	1
Glaucoma	2
Disc edema	2
Disc pallor	1
Non-proliferative diabetic retinopathy	2
Proliferative diabetic retinopathy with VH	1

gan transplantation, protracted neutropenia, immunosuppressive and corticosteroid therapy, iron overload or hemochromatosis, deferoxamine or deferoxamine therapy, voriconazole prophylaxis for transplant recipients, severe burns, an acquired immunodeficiency syndrome (AIDS), intravenous drug abuse and malnutrition [11].

Mucormycosis can involve the nose, sinuses, orbit, central nervous system (CNS), lung (pulmonary), gastrointestinal tract (GIT), skin, jaw bones, joints, heart, kidney, and mediastinum (invasive type), but ROCM is the commonest variety seen in clinical practice worldwide [12, 13]. As the spores enter the nasopharynx, tissue invasion, thrombosis, and necrosis spread from the nose to the PNS, orbit, and CNS. Before the pandemic, the prevalence was estimated to be between 0.005 and 1.7 per million people worldwide. But the second wave of COVID-19 had seen a surge of mucormycosis.

Neutropenia patients and those with malfunctioning phagocytes are susceptible to developing invasive mucormycosis because it is known from the pathophysiology of mucormycosis that mononuclear and polymorphonuclear phagocytes of healthy hosts kill Mucorales by producing oxidative metabolites and defensins [14].

Due to the immunosuppression caused by both the virus and the corticosteroids used in treatment, COVID-19 creates a hypoxic environment with high glucose, high ferritin, and attenuated phagocytic activity of leukocytes. This environment is ideal for the spores of various fungi to grow and spread [15]. Recent research has shown that COVID-19 is a pro-coagulable condition and that thrombotic events are more common [16].

This pro-coagulable state offers the ideal environment for mucor invasion caused by vascular thrombosis, which can result in widespread infections.

The study conducted by Sen et al.15 revealed that the male preponderance during the presentation of ROCM was comparable, with a mean age of 50.3 years. They attributed this to more outside exposure in men and suggested that fungal spores may be the possible cause.

Risk factors

92.8% of patients were diabetic, out of which 47.6% were uncontrolled DM, which was the major independent risk factor in our study. In a series of 41 cases, John et al.17 reported that 93% of the patients had DM. At the same time, Singh et al. [18] and Hoenigl et al. [19] observed that diabetics accounted for 80% of cases and that simultaneous ketoacidosis was found in 15% to 41% of patients. 80.3% of these cases were uncontrolled DM, and 90-97% were type 2 diabetics [19].

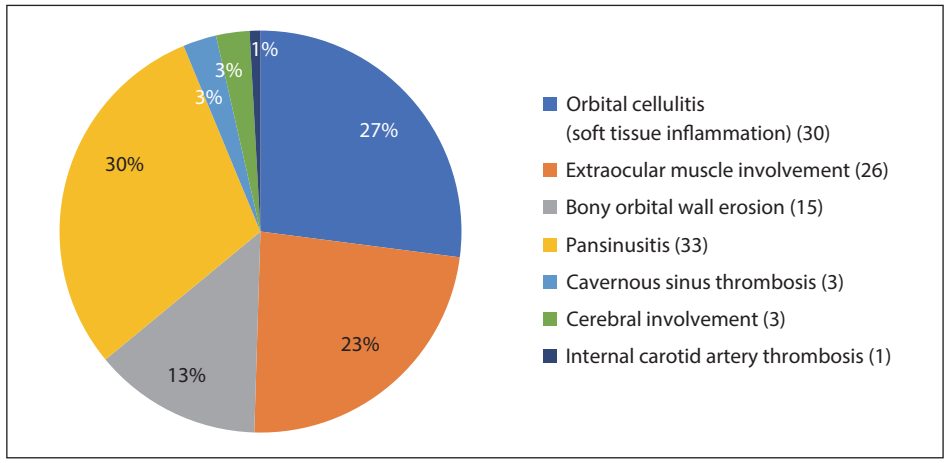

FIGURE 3. Radiological imaging findings

Table 3. Mucormycosis treatment

Treatment	Number of patients (percentage)
AMB *i.v.* (liposomal)	42
AMB *i.v.* + posaconazole/isuvaconazole	15
Sinus debridement	33
Exenteration	4
Retrobulbar liposomal amphotericin-B	11
Craniotomy	3

i.v. — intravenous; AMB — amphotericin B

Immunocompromised patients are more likely to develop mucormycosis when receiving a cumulative dose of more than 600 mg of prednisolone and 2–7 g of methylprednisolone.5 In our study, 83.3% of the patients were given steroids, but the dosage and time of administration during COVID-19 management were unknown. According to other studies, 76% of individuals with COVID-19-associated ROCM reported using systemic corticosteroids in the past, and a study done by Sen et al. [15] data revealed that systemic corticosteroids were used in 87% of the patients. Thus proposition is that irrational or injudicious use of corticosteroids can be a possible cause for ROCM.

Even though 71.4% of patients received oxygen treatment during COVID-19 management, we don't know the type of oxygen requirement in these patients, so this data is not comparable to other studies.

Clinical presentation

In a collaborative study done by Sen at al. [15], 10 days from the day of COVID-19 diagnosis was the median amount of time it took to diagnose mucormycosis. The duration was 14.5 days for those who showed signs of mucormycosis following a diagnosis of COVID-19.19. In contrast, in our study, it was 20 days. This delayed presentation may be because of the late identification of symptoms and less access to healthcare facilities in rural areas.

The most common non-ocular presenting symptom in our data was nasal stuffiness (95.2%). Orbital/facial swelling and pain was the most common ocular symptom seen in78.5%, followed by ptosis (54.7%), Loss of vision/diminution of vision (57.1%),

Headache (47.6%), proptosis (35.7%). In a meta-analysis done by Battacharya et al. [20] the most common presenting features were proptosis (60.6%), lid edema (60.7%), ophthalmoplegia (57.3%), loss of vision (53.7%), facial edema (34.7%), and ptosis (4 studies, 72.7%). Similar signs and symptoms are also seen in a study by Sen et al. [15].

CNS involvement has been identified in 37% of the cases of COVID-19-associated ROCM in a study [19], and in 21% (573 out of 2669 patients) patients in another collaborative study [15]. In our study, 7.1% (3 of 42) of patients had cerebral involvement, and 1 had internal carotid artery thrombosis.

Diagnosis and imaging

A quick clinical examination and sample collection from the nasal cavity are possible with diagnostic nasal endoscopy (DNE). With KOH wet mounts and calcofluor white, direct microscopy can quickly diagnose mucormycosis, which was

done in 88.8% of cases by Sen et al. [15]. In our study following DNE, direct microscopy was done in all patients. The patients with negative swabs but with clinical and radiological evidence of ROCM turned positive with a direct sinus sample obtained during debridement.

Despite the fact that contrast-enhanced MRI is the preferred imaging technique in other research [15], contrast-enhanced CT scan was also preferred in some studies21 and done in most of the patients in our study as well.

Because it is relatively faster, can be used for even unstable patients, and is also cost-effective. MRI was preferred in cases where extensive orbital and CNS involvement was suspected. In a retrospective analysis21 of 34 patients, 18 patient's orbital changes on CT, 3 patients had an intracranial disease, and 2 had cavernous sinus thrombosis. Similarly, in our study, also 30 had orbital cellulitis, 26 had EOM involvement, 3 had cerebral involvement like brain abscess, 3 had cavernous sinus thrombosis, and 1 had internal carotid artery thrombosis.

Management

An early diagnosis and rapid, well-coordinated, multidisciplinary care were essential to save the patient's life and sight. Over time, the mainstays of managing rhino-orbital mucormycosis have remained microbiological diagnosis, control of the underlying systemic condition, and antimicrobial therapy with debridement of necrotic tissue. If properly handled, exenteration may not be essential [22].

When possible, surgery should be considered with liposomal AMB as the first-line therapy for the treatment of mucormycosis, according to Brunet and Rammaert [23]. In our study, *i.v.* AMB was given to all the patients, where 40 received a liposomal form, and 2 received a deoxycholate form. 35.8% of patients was given combined therapy with posaconazole due to the non-availability of AMB initially. In other literature, it has been used in 88% of the patients in one study [19] and 73% of the patients in another [15] because of logistic reasons.

Posaconazole is a highly effective salvage therapy for ROCM, with life salvage and full resolution occurring in 67% of patients, according to an Indian study [24]. However, there is no evidence to support the use of combination therapy, and none of the primary treatment guidelines recommend it [25, 26].

According to specific case reports, an intraorbital injection of AMB deoxycholate at a dosage of 3.5 mg/mL can help save both life and the eye of the patient [27–29]. In our study, 11 patients in stage 2 were given retrobulbar liposomal AMB along with systemic AMB and sinus debridement. These patients had orbital cellulitis with EOM involvement on imaging. This was mainly considered a salvage procedure in patients with good vision and recovering patients following sinus debridement. Higher levels of the drug can reach the affected areas when directly injected into the orbit [12, 15–17]. On follow-up, all these patients were doing well with residual EOM restriction on examination with preserved vision. We observed minimal redness and chemosis in all patients, but it eventually resolved in a few days.

PNS debridement serves both diagnostic and therapeutic purposes15. In our study, sinus debridement was performed in 78.6% of patients. Whereas in a study by Sen et al. [15], PNS debridement was performed in 67% overall, and 27 of 34 patients underwent the same in a survey by Nithyanandam et al. [21].

Orbital exenteration was done in 4 patients in our study and performed simultaneously with FESS. In all these 4 cases, the involved eye had no visual potential, with diffuse orbital involvement. Along with that, one had disease limited to the orbit with minimal extension to the cavernous sinus. Similar criteria are also followed in other studies where 9 out of 34 patients [21] and 37% required orbital exenteration with extensive sinus debridement [15]. There is no definite agreement on the timing of orbital exenteration. Hence the treating physician should make the decision based on the clinical scenario of the individual patient. There is no discernible difference between survival with and without orbital exenteration [30, 31].

CONCLUSION

Middle-aged and older males are most commonly affected by COVID-19 associated ROCM, and most patients experience the beginning of ROCM symptoms between day 20 and day 30 following the diagnosis of COVID-19. The delayed presentation can occur for up to 2 months. Two months of post-COVID-19 follow-up are advised, maybe in the setting of a formal post-COVID-19 follow-up clinic. DM and corticosteroids are reliable, significant, and separate risk factors for ROCM related to COVID-19. In a patient with COVID-19, glycemic control is crucial.

The typical symptoms and signs include periorbital and facial pain and edema, stuffiness, proptosis, ptosis, and diminished vision. The common clinical symptoms and signs should be recognised right away. Then a diagnostic nasal endoscopy, an endoscope-guided nasal swab for microbiological assessment, and a nasal microbiopsy for quick histopathology should be performed to make an accelerated diagnosis. The preferred imaging method is contrast-enhanced MRI; without this, a CT scan is advised. A group of doctors with different specialties should stage, prioritize, and manage ROCM.

COVID-19-related ROCM requires a combined effort from multidisciplinary medical teams and the government. It needs to be addressed as aggressively as COVID-19 itself. We can anticipate seeing ROCM in the days to come considering the fact that Indians naturally have a greater frequency of DM. The tropical climate predisposes to mucormycosis, and moderate to severe cases of COVID-19 will need corticosteroids for life salvage. The construction of well-equipped, specialised regional hubs of multifunctional ROCM management centres, each connected to COVID-19 treatment facilities, and logistical preparation to ensure an adequate supply of AMB could help save these patients' lives and eyes.

Conflict of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Funding

None declared.

Patients' consent

The authors certify they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published, and due efforts will be made to conceal their identity.

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