Original Article

A clinical study of rhino-orbital-cerebral mucormycosis during the COVID-19 pandemic in western Maharashtra

Varsha Vivek Manade, Megha R. Kotecha

Department of Ophthalmology, Dr. D.Y. Patil Medical College and Hospital, Pimpri, Pune, Maharashtra, India

Abstract

Background: The aim of the study was to describe the epidemiology and study the risk factors, clinical presentation, management, and outcome of rhino-orbital-cerebral mucormycosis (ROCM) in terms of mortality, exenteration, eye salvage, and vision salvage. **Methods:** This retrospective, observational study was carried out over a period of two months. A detailed history was noted, and an ophthalmological examination was done. The diagnosis was done by Potassium hydroxide (KOH) mount and fungal culture. Magnetic resonance imaging (MRI) of the orbit, brain, and paranasal sinuses were performed. Medical (intravenous amphotericin B, posaconazole), surgical (retrobulbar amphotericin B injection, exenteration, Functional Endoscopic Sinus Surgery (FESS)), or combined management was evaluated, and clinical outcomes was noted. **Results:** The mean age of patients was 54.2 years and the male-to-female ratio was 1.77/1. The most common underlying risk factor for ROCM was uncontrolled diabetes mellitus (70%), followed by the use of corticosteroids for the management of coronavirus disease 2019 (COVID-19) infection in 68% of patients. The most common clinical presentation was diminution of vision followed by eschar, ptosis, and proptosis. Medical and FESS were done in all patients; exenteration was done in 12% of patients. Sixty-six percent of patients were alive with regression of ROCM, 20% of patients were alive with residual, 8% of patients were alive with the progression of ROCM, and 6% of patients had expired. Among the ones who are alive, the ocular outcome was orbital exenteration in 12.76%, the eye was salvaged in 25.53 and vision salvage was achieved in 61.70%. **Conclusion:** ROCM affects older males. Immunosuppression due to COVID-19 infection, diabetes mellitus, and corticosteroid use in the management of COVID-19 are the main risk factors for the development of ROCM. Antifungal therapy along with surgical debridement decreases mortality.

Keywords: Amphotericin B, COVID-19, exenteration, posaconazole, rhino-orbital-cerebral mucormycosis, vision salvage

Introduction

Coronavirus (2019-nCoV) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in 2019 in Wuhan, China. It quickly spread to other parts of the world, resulting in a global pandemic.[1] It resulted in a wide range of disease patterns, ranging from mild rhinitis to life-threatening pneumonia. Multiple factors including systemic immune alterations of the coronavirus disease 2019 (COVID-19) infection, pre-existing diseases, and the use of immunosuppressive therapy may lead to secondary infections. India has a high prevalence rate of diabetes mellitus (DM) type II (8.9% of adults, 77 million patients), which is a well-known risk factor for mucormycosis. Mucormycosis is an aggressive, rapidly progressive, and life-threatening fungal infection. Extensive angioinvasion with resultant vessel thrombosis and tissue necrosis is a hallmark of mucormycosis.[2]

An increased number of mucormycosis cases have been reported in patients with COVID-19 infection worldwide. In 2019–2020 globally, the prevalence of mucormycosis varied from 0.005 to 1.7 per million population, while its prevalence is nearly 80 times higher (0.14 per 1000) in India compared to developed countries.[3-5]

Address for correspondence: Dr. Megha R. Kotecha, Dr D Y Patil, Medical College Hospital and Research Centre, A2, 203, Mahindra Antheia, Neharunagar, Pimpri - 411 018, Pune, Maharashtra, India.
E-mail: megharkotecha@gmail.com

Received: 01-01-2024 **Revised:** 20-03-2024
Accepted: 29-03-2024 **Published:** 11-09-2024

Access this article online

Quick Response Code:

Website: http://journals.lww.com/JFMPC

DOI: 10.4103/jfmpc.jfmpc_2_24

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Manade VV, Kotecha MR. A clinical study of rhino-orbital-cerebral mucormycosis during the COVID-19 pandemic in western Maharashtra. J Family Med Prim Care 2024;13:3730-4.

The highest number of mucormycosis cases have been reported in India. Mucormycosis affects immunocompromised individuals including those with uncontrolled DM, iatrogenic immunosuppression, organ transplant, and hematological malignancies. India has a large number of people with DM, which is the most common risk factor for mucormycosis.[6]

A definitive diagnosis of mucormycosis is done by histological examination. Depending on the site of infection and underlying predisposing factors, mortality rates may vary from 10% to 100%. Early diagnosis and immediate intervention are crucial for such patients. Treatment includes control of the underlying disease, surgical debridement, and systemic antifungal therapy. We have observed the sudden rise of mucormycosis cases in the COVID-19 era.

Management of COVID-19 includes the use of steroids, remdesivir, tocilizumab, and oxygen supplementation depending upon the severity of the disease. In this study, we saw an association of these factors along with other comorbidities with a rise in rhino-orbital-cerebral mucormycosis (ROCM) cases. We evaluated the epidemiology, risk factors, and clinical presentation of the disease in concurrent or post COVID ROCM patients. Management of these patients and clinical outcomes in terms of surgical intervention with regard to eye salvage or vision salvage and mortality were noted. With COVID-19 infection, especially in patients with pre-existing risk factors, early diagnosis and treatment help in the prevention of disease with the subsequent reduction of mortality and morbidity.

Methodology

This prospective observational study was carried out at a tertiary health care center in western Maharashtra. Institutional ethics committee approval was obtained. Fifty confirmed rhino-orbital mucormycosis cases were included in this study. Written informed consent was obtained from all patients. All patients were studied over a period of two months.

A detailed history was noted including DM, other comorbidities, history of use of steroids, oxygen supplementation, injection remdesivir, and ventilatory support during their COVID-19 management. Symptoms and signs were recorded. A comprehensive ophthalmological examination was done for all patients including distant visual acuity testing, torch light examination, slit lamp examination (if the patient is mobile), and fundus examination by direct and indirect ophthalmoscope. A provisional diagnosis of rhino-orbital mucormycosis was performed.

A deep nasal swab and tissue from diagnostic nasal endoscopy were sent for KOH mount, and fungal culture and diagnosis were confirmed. Magnetic resonance imaging (MRI) of the orbit, brain, and paranasal sinuses was performed to assess the extent of the disease.

Medical (intravenous amphotericin B, Posaconazole), surgical (retrobulbar amphotericin B injection, exenteration, FESS), or combined management was evaluated and clinical outcome was noted in terms of mortality, exenteration, eye salvage, and vision salvage. Data were collected and entered into a Microsoft Excel sheet, and analysis was done using Epi Info 7 software. The descriptive statistics were presented as frequencies, mean, or median, as appropriate.

Results

A total of 50 patients diagnosed with mucormycosis were included in this study. In this study, the most common age group was 51–60 years of age with a mean age of 54.2 years, and 32 were males and 18 were females.

Most of the patients had underlying risk factors. DM was among the most common risk factors and was present in 60% of patients. Seventy percent of patients had uncontrolled DM and the mean Glycated hemoglobin (HbA1c) was 7.7.

One patient had chronic kidney disease, for which he was on hemodialysis treatment.

COVID-19 infection management-associated risk factors for rhino-orbital mucormycosis included a history of use of steroids, remdesivir, interleukin (IL)-6 inhibitor, home oxygen supplementation, hospital oxygen supplementation, and ventilatory support. Systemic corticosteroids were used in 68% of patients, out of which six (17.64%) patients received oral steroids, eight (23.52%) patients received injection dexamethasone, and 20 (58.82%) patients received injection methylprednisolone [Figure 1]. Twenty-six percent of patients received remdesivir, 4% of patients received IL-6 inhibitors, 34% of patients received oxygen supplementation at the hospital, and 6% of patients required ventilatory support [Figure 2].

The most common presentation was a diminution of vision which was observed in 86%. Eschar and ptosis were seen in 78% of patients, followed by proptosis (74%), ophthalmoplegia (70%), and nose bleeds (38%). Central retinal artery occlusion was seen in 38% of patients [Figure 3].

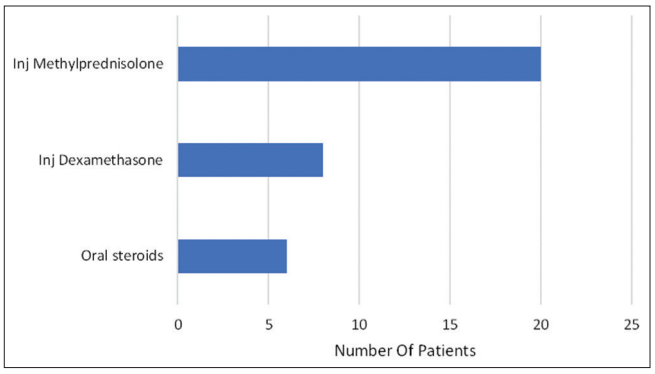

Figure 1: Steroid use for the management of COVID-19

Only 14% of patients had normal vision 6/6. Twelve percent of patients had vision between 6/36 and 6/9. Twenty-eight percent of patients had vision of ≤6/60. Twelve percent of patients had perception of light present and projection of rays accurate, 8% of patients had PR inaccurate, 22% of patients could not appreciate the light, and 4% of patients vision could not be assessed.

Paranasal sinus involvement was seen in 100% of patients. Orbital involvement was seen in 76% of patients with orbital apex involvement in 58% of patients. Involvement of cavernous sinus involvement was observed in 12% of patients and Central Nervous System (CNS) involvement was seen in 14% of patients.

All patients received intravenous amphotericin B for a mean period of 22.08 days. Thirty-nine patients received deoxycholate amphotericin B, while 11 patients received liposomal amphotericin B. Sixty-six percent of patients received retrobulbar amphotericin B injection. Functional endoscopic sinus surgery was performed in all patients. Exenteration was done in 12% of patients. Combined FESS and exenteration were performed in 12% of patients. Sinus irrigation with amphotericin B was done in 32% of patients [Figure 4].

Sixty-six percent of patients were alive with regression of ROCM, 20% of patients were alive with residual ROCM, 8% of patients were alive with progression of ROCM, and 6% of patients had expired [Figure 5].

Among the ones who are alive, an ocular outcome was available. Six patients had orbital exenteration, 12 patients' eyes were salvaged, and 29 patients' vision salvage was achieved [Table 1].

Six patients had exenteration, eight patients could not appreciate the light, three patients had projection of rays inaccurate, 13 patients had vision ≤6/60, and 10 patients had vision between 6/36 and 6/9 [Table 2].

Discussion

Mucormycosis is an opportunistic, angioinvasive fungal infection caused by *Mucorales* species of fungi. It has many predisposing factors such as uncontrolled DM, corticosteroids, or other immunosuppressive therapy. Also, primary or secondary immunodeficiency, hematological malignancies, hematological stem cell transplantation, solid organ malignancies, solid organ transplantation, and iron overload are other predisposing factors.[7]

In December 2019, the COVID-19 pandemic started in Wuhan, China, and spread worldwide. COVID-19 infection is associated with a decreased number of lymphocytes which in turn results in the body's cellular immune function.[8]

Immunosuppression is caused by COVID-19 and the use of corticosteroids in its management. COVID-19

Table 1: Final ocular outcome

Final Ocular Outcome	Number of Patients(%)
Exenteration	6 (12.76%)
Eye salvage	12 (25.53%)
Vision salvage	29 (61.70%)

Table 2: Final visual acuity

Final Visual Acuity	Number of Patients
Exenteration	6
PL negative	8
PR inaccurate	3
≤6/60	13
6/36–6/9	10
>6/9	7

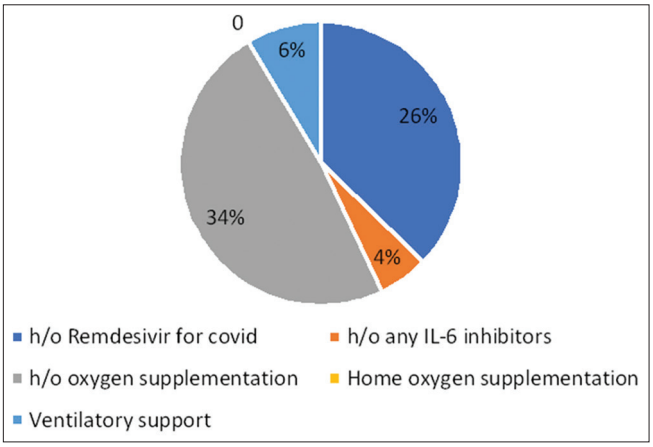

Figure 2: Management of COVID-19

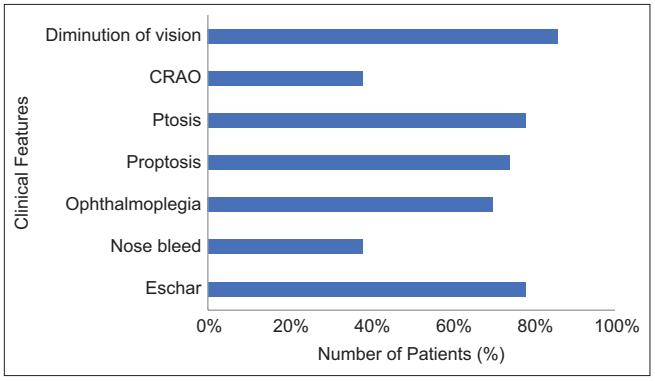

Figure 3: Clinical features of ROCM

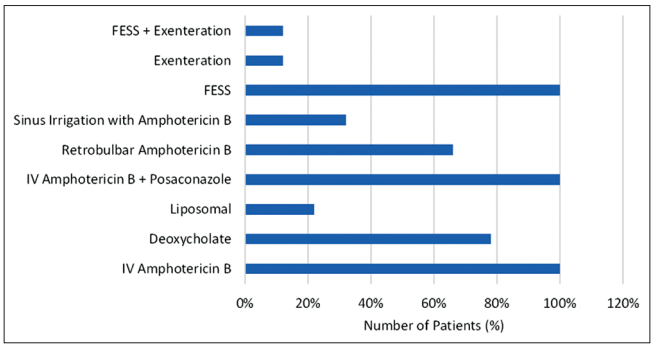

Figure 4: Overall management of ROCM

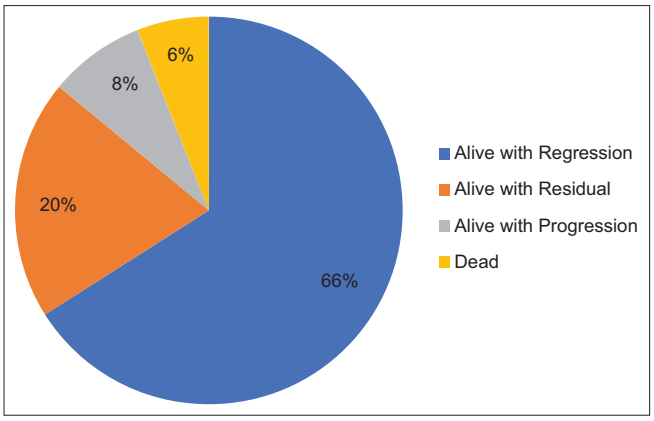

Figure 5: Final systemic outcome

produces a hypoxic environment with high glucose levels, which is highly suitable for the fungal spores to germinate and proliferate.[6]

A total of 50 patients diagnosed with mucormycosis with previous or concurrent COVID-19 infections were studied. The maximum number of patients belongs to the age group of 51–60 years with a mean age of 54.2 years. In our study, there was male predilection with a male-to-female ratio of 1.77/1. The demographic profile is consistent with the study by White *et al.*[9]

In our study, DM was present in 60% of patients, out of which 70% had uncontrolled DM. The commonest risk factor associated with ROCM in our study is DM. The results are similar to those of studies by Yohai *et al.*[10] and Ferry *et al.*[11]

In our study, 68% of patients received corticosteroids for the management of COVID-19 infection with injection of methylprednisolone being the most commonly used followed by injection of dexamethasone and oral corticosteroid. A study by Lionakis[12] showed that a cumulative dose greater than 2–7 g of methylprednisolone and 600 mg of prednisone has been found to predispose immunocompromised patients to mucormycosis. Similarly, in our study, corticosteroid use for the management of COVID-19 infection is one of the contributing factors to the development of mucormycosis. Twenty-six percent of patients received remdesivir, 4% received IL-6 inhibitors, 34% received oxygen supplementation at the hospital and 6% required ventilatory support for the management of the COVID-19 infection. Their percentage is less and most of them had DM and were on corticosteroid treatment for COVID-19. All the above factors may not have played a role in increasing the risk of ROCM. There are no similar studies reported to compare the results.

The most common symptoms and signs reported in our study were diminutions of vision (86%), escher (78%), ptosis (78%), proptosis (74%), and ophthalmoplegia (70%). Nose bleeds and Central Retinal Artery Occlusion (CRAO) were seen in 38% of patients. Paranasal sinus involvement was seen in 100% of patients, and orbital involvement was seen in 76% of patients with orbital apex involvement in 58% of patients. Involvement of cavernous sinus was seen in 12% of patients and involvement of the CNS was observed in 14% of patients, which is lower as compared to the study by Hoenigl *et al.*[13] in which CNS involvement was documented in 37% of the cases of COVID-19-associated ROCM.

The management of ROCM included medical management and surgical management. All patients received amphotericin B either deoxycholate or liposomal. Seventy-eight percent of patients received deoxycholate amphotericin B, while 22% patients received liposomal amphotericin B. Liposomal amphotericin B was used mostly in patients with CNS involvement as it crosses the blood-brain barrier effectively and in patients of chronic kidney disease. In a study by Hoenigl *et al.*,[13] amphotericin B was used in 88% of the patients with COVID-19-associated ROCM, which is comparable to our study. The survival rate of patients dramatically increased after the introduction of amphotericin B.[14]

Combined amphotericin B and posaconazole were received by very few patients (3%). A study by Manesh *et al.*[15] showed posaconazole is highly effective as salvage therapy for ROCM with life salvage and complete resolution in 67% of the patients. However, there are no data supporting the use of combination therapy, and has not been recommended in any of the major treatment guidelines.[3,16,17]

In our study, 52% of patients received retrobulbar amphotericin B injection which resulted in eye salvage and vision salvage. Studies by Lee *et al.*,[18] Hirabayashi *et al.*,[19] and Safi *et al.*[20] have shown retrobulbar amphotericin B injection is effective for eye salvage and life salvage but sufficient data is not available regarding its safety and vision salvage.

Functional endoscopic sinus surgery was done in all patients, exenteration was performed in 12% of patients, and combined FESS and exenteration were done in 12% of patients.

In our study, posaconazole was given as maintenance antifungal therapy after the completion of amphotericin B treatment. Six percent of patients could not be revived.

In our study, mortality associated with ROCM was 6%. In addition, disease progression was seen in 8% of patients; 66% of patients had regression while 20% of patients had residual disease. The mortality rate in our study was less as compared to other studies. A study by Hoenigl *et al.*[13] and Prakash and Chakrabarti[21] showed ROCM is associated with a 30–90% mortality rate in cases with cerebral involvement. A study by Singh *et al.*[6] showed that in cases associated with COVID-19, the overall mortality has been estimated to be 31%.

Conclusion

ROCM affects older males. Immunosuppression due to COVID-19 infection, DM, and corticosteroid use in the management of COVID-19 are the main risk factors for the development of ROCM. Antifungal therapy along with surgical debridement decreases mortality. The limitation of the study is less sample size. A prospective study with a large sample size is required in the future.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Farnoosh G, Alishiri GH, Hosseini Zijoud SR, Dorostkar R, Farahani AJ. Understanding the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) and coronavirus disease (COVID 19) based on available evidence—A narrative review. J Mil Med 2020;22:1–11.
2. Bouchara JP, Oumeziane NA, Lissitzky JC, Larcher G, Tronchin G, Chabasse D. Attachment of spores of the human pathogenic fungus Rhizopus oryzae to extracellular matrix components. Eur J Cell Biol 1996;70:76–83.
3. Skiada A, Pavleas I, Drogari-Apiranthitou M. Epidemiology and diagnosis of mucormycosis: An update. J Fungi 2020;6:265.
4. Chander J, Kaur M, Singla N, Punia RPS, Singhal SK, Attri AK, *et al.* Mucormycosis: Battle with the deadly enemy over a five-year period in India. J Fungi (Basel) 2018;4:46.
5. Prakash H, Chakrabarti A. Global epidemiology of mucormycosis. J Fungi (Basel) 2019;5:26.
6. Singh AK, Singh R, Joshi SR, Misra A. Mucormycosis in COVID 19: A systematic review of cases reported worldwide and in India. Diabetes Metab Syndr 2021;15:102146.
7. Sen M, Lahane S, Lahane TP, Parekh R, Honavar SG. Mucor in a viral land: A tale of two pathogens. Indian J Ophthalmol 2021;69:244-52.
8. Chen N, Zhou M, Dong X. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet 2020;395:507–13.
9. White PL, Dhillon R, Cordey A, Hughes H, Faggian F, Soni S, *et al.* A national strategy to diagnose COVID 19 associated invasive fungal disease in the ICU. Clin Infect Dis 2021;73:e1634-44.
10. Yohai R, Bullock J, Aziz A, Markert R. Survival factors in rhino-orbital-cerebral mucormycosis. Surv Ophthalmol 1994;39:3–22.
11. Ferry A, Abedi S. Diagnosis and management of rhino orbito-cerebral mucormycosis (phycomycosis)-A report of 16 personally observed cases. Ophthalmology 1983;90:1096-104.
12. Lionakis MS, Kontoyiannis DP. Glucocorticoids and invasive fungal infections. Lancet 2003;362:1828-38.
13. Hoenigl M, Seidel D, Carvalho A, Rudramurthy SM, Arastehfar A, Gangneux JP, *et al.* The emergence of COVID 19 associated mucormycosis: Analysis of cases from 18 countries. Lancet Microbe 2022;3:e543-52.
14. Furco A, Mouchet B, Carbonnelle M, Vallerand H. Pulmonary mucormycosis: Benefit of aerosol amphotericin B. Rev Mal Respir 2001;18:309–313.
15. Manesh A, John AO, Mathew B, Varghese L, Rupa V, Zachariah A, *et al.* Posaconazole: An emerging therapeutic option for invasive rhino-orbito-cerebral mucormycosis. Mycoses 2016;59:765-72.
16. Cornely OA, Alastruey-Izquierdo A, Arenz D, Chen SC, Dannaoui E, Hochhegger B, *et al.* Global guideline for the diagnosis and management of mucormycosis: An initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. Lancet Infect Dis 2019;19:e405-21.
17. Sipsas NV, Gamaletsou MN, Anastasopoulou A, Kontoyiannis DP. Therapy of mucormycosis. J Fungi 2018;4:90.
18. Lee AS, Lee PW, Allworth A, Smith T, Sullivan TJ. Orbital mycoses in an adult subtropical population. Eye 2020;341640-7.
19. Hirabayashi KE, Kalin-Hajdu E, Brodie FL, Kersten RC, Russell MS, Vagefi MR. Retrobulbar injection of amphotericin B for orbital mucormycosis. Ophthalmic Plast Reconstr Surg. 2017;33:e94-7.
20. Safi M, Ang MJ, Patel P, Silkiss RZ. Rhino-orbital-cerebral mucormycosis (ROCM) and associated cerebritis treated with adjuvant retrobulbar amphotericin B. Am J Ophthalmol Case Rep 2020;19:100771.
21. Prakash H, Chakrabarti A. Epidemiology of mucormycosis in India. Microorganisms 2021;9:523.