Original Article - Prospective Study

Osteomyelitis of the Jaw Due to Mucormycosis after Coronavirus Disease 2019 Infection - A Prospective Study

Abhay Datarkar, Amit Bhawalkar, Vartik Shah, Varsha Manekar, Vandana Gadve, Surendra Daware, Damyanti Walkey, Francesca Gioia[1], Julio Acero[2]

Department of Oral and Maxillofacial Surgery, Government Dental College and Hospital, Government Medical College Premises, Nagpur, Maharashtra, India, [1]Department of Infectious Disease, University Hospital Ramon y Cajal, IRYCIS and CIBER, [2]Department of Oral and Maxillofacial Surgery, Ramón y Cajal and Puerta de Hierro University Hospitals, University of Alcala, IRYCIS, Madrid, Spain

Abstract

Introduction: The objective of the study was to describe the incidence, clinical characteristics, treatment and outcome of patients with rhinocerebral coronavirus disease 2019-associated mucormycosis (CAM). **Materials and Methods:** We performed an unicentric observational study. A total of 113 cases of CAM were evaluated from January 2021 to June 2021. We described the overall incidence of CAM in Nagpur district up to June 2021, the clinical presentation of CAM, the subtype of CAM, the laboratory diagnosis, the type of surgical management in CAM, the pre-operative and 3-month post-operative C-reactive protein marker values, the post-operative healing and complications and the mortality rate. **Results:** The mean age of the patients was 38.8 years. Rhinomaxillary subtype was the most common. All patients underwent medical as well as surgical intervention as the treatment modality. There was mortality in two patients. **Discussion:** Study highlights the need for physicians to closely monitor coronavirus disease 2019 (COVID-19) patients, especially severe cases with pre-existing diabetes/receiving corticosteroid therapy and the need for patient education as early diagnosis and prompt treatment leads to better prognosis.

Keywords: Amphotericin B, coronavirus disease 2019 associated mucormycosis, coronavirus disease 2019, maxillectomy, surgical debridement

Introduction

Mucormycosis (MCR) is a highly invasive fungal infection caused by genera *Rhizopus, Mucor*, *Rhizomucor*, *Cunninghamella, Lichtheimia* and *Apophysomyces*. The main clinical forms of MCR include: rhinocerebral, pulmonary, cutaneous, disseminated and gastrointestinal. There have been a number of fungal superinfections associated with Coronavirus disease 2019 (COVID-19) described in the literature, with pulmonary aspergillosis being the most common. However, MCR has emerged as a significant issue, especially in India, and intensive care unit rates of invasive candidiasis are higher than that seen before COVID-19.[1,2]

MCR can lead to devastating complications such as invasion of the paranasal sinuses, resulting in necrosis of the nasal mucosa, turbinates and palate. If left untreated or undetected, the infection can progress throughout the face, causing necrosis of facial bones and potentially penetrating into the orbits and cranium, leading to mortality. While osteomyelitis of the maxilla is typically rare due to its abundant blood supply and thin cortical plates, the high angio-invasiveness potential of *mucor* fungi affects the endothelial lining of blood vessels, causing vascular insufficiency and bone necrosis resulting in osteomyelitis.[3]

Different theories are emerging to explain the pathogenesis of coronavirus disease 2019-associated mucormycosis (CAM). Diabetes mellitus (DM) is an important comorbidity that complicates the management of COVID-19. Increasing insulin resistance due to cytokine storm, as well as a high expression

Access this article online

Quick Response Code:

Website: https://journals.lww.com/aoms

DOI: 10.4103/ams.ams_16_24

Address for correspondence: Dr. Vartik Shah, Department of Oral and Maxillofacial Surgery, Government Dental College and Hospital, Government Medical College Premises, Medical Square, Nagpur - 440 003, Maharashtra, India.
E-mail: vartikm@gmail.com

Received: 06-02-2024 **Last Revised:** 09-05-2024
Accepted: 23-05-2024 **Published:** 19-07-2024

How to cite this article: Datarkar A, Bhawalkar A, Shah V, Manekar V, Gadve V, Daware S, *et al*. Osteomyelitis of the jaw due to mucormycosis after coronavirus disease 2019 infection - A prospective study. Ann Maxillofac Surg 2024;14:40-5.

of angiotensin-converting enzyme 2 receptors in pancreatic islets suggests a possible 'diabetogenic state' in severe acute respiratory syndrome coronavirus 2 infection.[4] In addition, severe COVID-19 can result in a hyperferritinaemia syndrome that results in damaged tissues and the release of free iron into the circulatory system.[5] The presence of iron overload and excess free iron in acidic states is one of the key and unique risk factors for MCR.[6] Furthermore, corticosteroids have been shown to be beneficial in some groups of patients with COVID-19 who have been hospitalised,[7] but they pose a significant risk factor for the development of invasive mould infections as MCR.[8]

The aim of our study was to describe all cases of COVID-19-associated rhinocerebral MCR in our centre to better understand the clinical characteristics, risks factors and the outcomes to understand the need for active surveillance strategies.

Materials and Methods

We performed a prospective unicentric observational study. We identified all cases of CAM with rhino-orbito-cerebral and rhino maxillary disease. We included all patients presenting to the Department of Oral and Maxillofacial Surgery over a period of 6 months (January 2021 to June 2021). Inclusion criteria of the study were all reported cases of proven rhino-orbital-cerebral and rhino maxillary MCR, 3 months after diagnosis of COVID-19 infection. All the patients were reverse transcription-polymerase chain reaction (PCR) proven cases of past COVID-19 infection with no active COVID-19 infection. Exclusion criteria were patients diagnosed with MCR with a negative history of COVID-19 infection, bacterial or other fungal osteomyelitis and patients who are not reporting for follow-up.

Ethical Approval was given by the Institutional Ethical Committee Government Dental College and Hospital, Nagpur (Ref no. IEC/04/12). Written informed consent was obtained from all the patients before participating in this study. We performed descriptive analysis for the following parameters:

1. Overall incidence and distribution of CAM in Nagpur district up to June 2021
2. History of COVID-19 infection in all the patients reported to our centre with MCR
3. Clinical presentation of CAM
4. Subtype of CAM
5. Pattern of osteomyelitis in CAM: All patients underwent gadolinium contrast magnetic resonance imaging (MRI) and computed tomography (CT), peripheral nervous system (PNS) for knowing the extent of bone as well as soft-tissue involvement [Figure 1]
6. Laboratory diagnosis of fungal infection (potassium hydroxide preparation [KOH prep test]/Histopathology) [Figure 2]
7. Type of surgical management in CAM which included total maxillectomy, hemi-maxillectomy, partial-maxillectomy, anterior-maxillectomy, palatal resection, zygoma resection sequestrectomy, maxillary sinus debridement and functional endoscopic sinus surgery [Figures 3 and 4]
8. Pre-operative and 3 months post-operative C-reactive protein (CRP) marker for prognosis of CAM
9. Post-operative healing and complications
10. Mortality rate.

A specific institute-based protocol was devised for the patient reported with CAM in our centre [Figure 5]:[9] Dual drug antifungal therapy with amphotericin B and/or posaconazole was given in all diagnosed cases of rhino-orbital-cerebral CAM. Tablet posaconazole 300 twice daily was given as a loading dose, followed by 300 mg once daily for 3 months and injection amphotericin B (conventional/lipid complex) was given 3 days preoperatively and 7–15 days postoperatively. Surgical treatment was restricted to patients with polymerase chain reaction (PCR)-negative results for COVID-19. The surgical procedure was tailored according to each patient's findings and by extension of the infection.

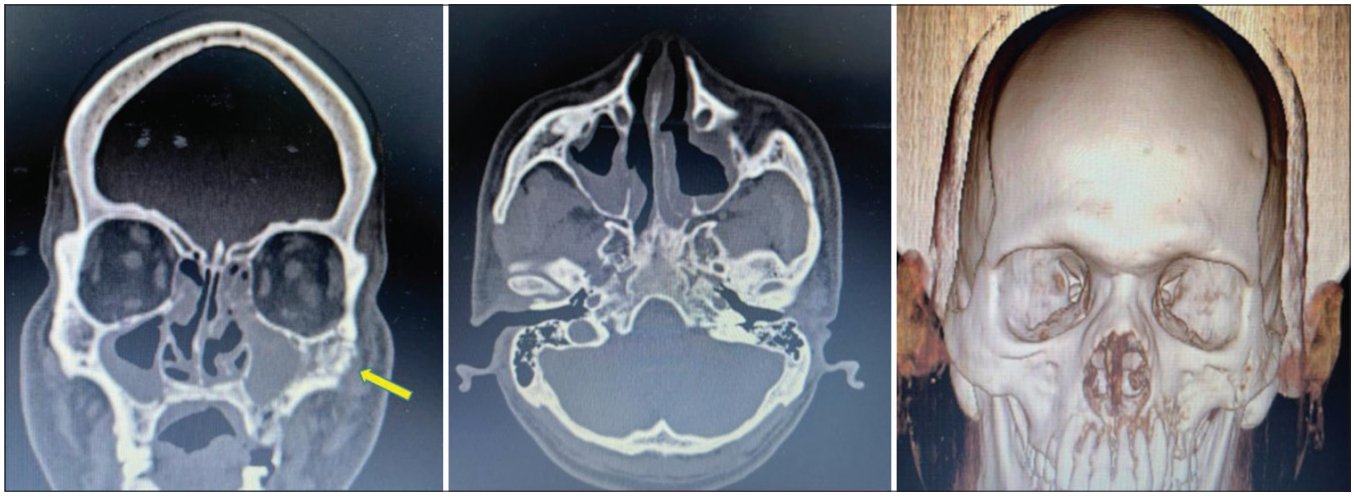

Figure 1: Three-dimensional computed tomography face images of a patient with rhinomaxillary mucormycosis with involvement of left zygoma

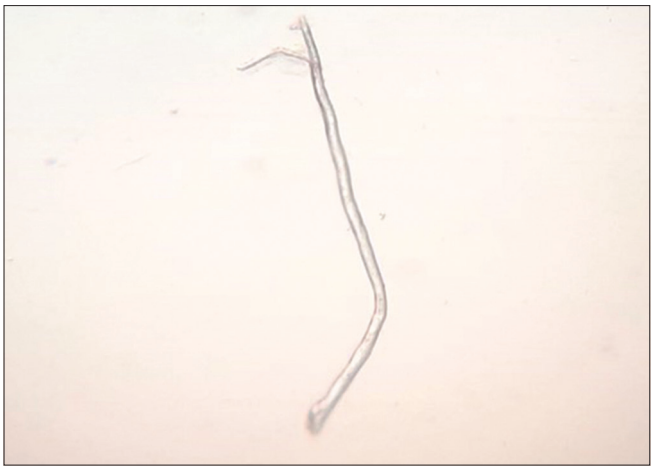

Figure 2: Potassium hydroxide mount of swab culture showing fungal hyphae with wide-angle branching suggestive of coronavirus disease 2019-associated mucormycosis

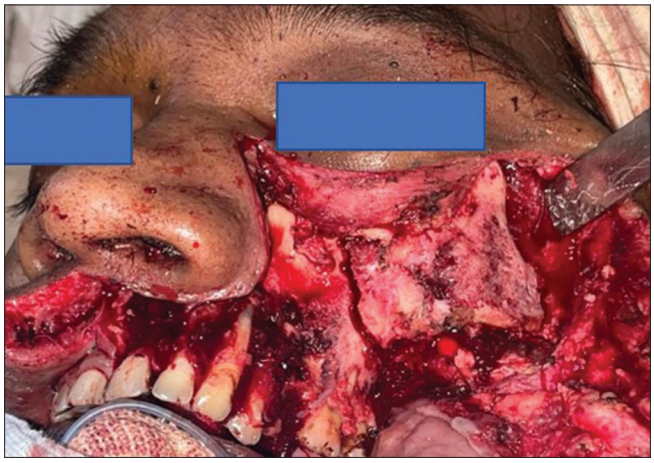

Figure 3: Intraoperative view of osteotomy cut for involved zygoma resection

Figure 4: Surgical specimen of resected total maxilla

Endoscopic, open and combined approaches were utilised with aggressive resection of the involved bone and sinus debridement (ethmoid, sphenoid, frontal and maxillary), followed by antifungal therapy to eradicate infection. Follow-up for patients who survived was maintained regularly for the first post-operative month.

Table 1: Patient characteristics

	n (%)
Total patients (*n*)	113
Male patients	73 (65)
Female patients	40 (35)
History of COVID-19 infections in patients reported with CAM	
Previously diagnosed case of COVID-19 infection	113 (100)
ICU admission during COVID-19 infection	29 (25)
Ward admission during COVID-19 infection	35 (31)
Supplemental oxygen therapy during treatment of COVID-19 infection	42 (37)
Type of steroids used during the treatment	103 (91)
Methylprednisolone	67 (65)
Prednisolone	6 (6)
Dexamethasone	30 (29)
Pre-existing/post-COVID-19 DM	55 (48)
Gap between discharge from hospital and development of CAM	
<1 month	40 (63)
1–2 months	20 (31)
>2 months	4 (6)

COVID-19: Coronavirus disease 2019, CAM: Coronavirus disease 2019-associated MCR, DM: Diabetes mellitus

Results

According to the official data by Nagpur Municipal Corporation (2021), a total of 1301 cases of CAM were reported in the Nagpur district till 7th June with total COVID-19 infections crossing more than 0.4 million.[10] We evaluated a total of 113 cases of MCR following COVID-19 infection who reported to our department [Table 1]. The mean age was 38.8 years, and the median age was 40 years. A total of 65% of all CAM infections occurred in males. During COVID-19 infection, intensive care was required in 25% (n = 29), and ward admission was required in 31% (n = 35) of cases. The rest of the patients (n = 49; 44%) were either under home isolation or treated on outpatient basis. Supplemental oxygen therapy was required in 37% (n = 42) of patients. A staggering number of 103 (91%) patients were under steroid therapy (IV/oral). Methylprednisolone was used in 65% (n = 67) patients, prednisolone was used in 6% (n = 6) patients and dexamethasone was used in 29% (n = 30). Pre-existing/post-COVID-19 DM was present in 48% (n = 55) of patients, whereas the gap between discharge from the hospital and development of CAM was less than 1 month in 63% (n = 40) of patients admitted in COVID hospitals, 1–2 months in 31% (n = 20) of the patients and more than 2 months in 6% (n = 4) of patients.

Intraoral findings observed in the patients were mobility of teeth in 53% (n = 60) cases, teeth pain in 57% (n = 64) cases, maxillary mobility in 29% (n = 33) cases, multiple draining sinuses in

31% (*n* = 35) cases, palatal fistula in 13% (*n* = 15) cases and exposed bone intraorally in 9% (*n* = 10) cases [Table 2]. Forty three percent (*n* = 49) of patients had nasal findings such as dark blood-tinged nasal discharge, pus discharge, nasal stiffness, perinasal oedema, pain and paraesthesia. Ocular findings which included pain and paraesthesia, periorbital oedema, proptosis, ptosis, loss of extraocular movements, fixed dilated pupil, decreased visual acuity and blindness were present in 11% (*n* = 12) patients. Neurologic findings were present in only 2% (*n* = 2) of the cases which included headaches, hemiparesis and focal seizures.

Rhinomaxillary subtype was present in 48% (*n* = 54) patients, the rhinonasal subtype was present in 39% (*n* = 45) patients, rhino-orbital subtype was present in 11% (*n* = 12) patients and rhino-orbito-cerebral in 2% (*n* = 2) patients. The lytic pattern was present in 22% (*n* = 25) patients, the sclerotic pattern was present in 5% (*n* = 6) patients, mixed pattern was present in 28% (*n* = 32) patients and sequestrum was present in 44% (*n* = 50) patients [Table 2]. KOH prep test of pus culture/swab culture showed fungal infection in 98% (*n* = 111) patients, whereas tissue biopsy in all the patients (*n* = 113) with signs and symptoms of MCR showed broad-based, ribbon-like, non-septate hyphae with wide-angle branching (approximately 90°) in the laboratory diagnosis, thus confirming the diagnosis of MCR.

Out of 113 patients, a total of 99 patients underwent surgical intervention. Surgical treatment was restricted to patients with PCR-negative results for COVID-19 [Table 3]. Total maxillectomy was done in 10% (*n* = 10) patients, hemi-maxillectomy was done in 5% (*n* = 5) patients, partial-maxillectomy was performed in 5% (*n* = 5) patients, anterior maxillectomy was done in 4% (*n* = 4) patients, isolated palatal resection was done in 2% (*n* = 2) patients, zygoma resection was done in 4% (*n* = 4) patients, sequestrectomy was done in 14% (*n* = 14) patients, maxillary sinus debridement (Caldwell-Luc approach) was done in 14% (*n* = 14) patients and functional endoscopic sinus surgery were performed in the department of ENT in 41% (*n* = 41) patients which were referred by us.

Twelve patients with rhino-orbital CAM were referred to the Department of Ophthalmology and 2 patients with rhino-orbito-cerebral CAM were referred to the Department of Neurosurgery for further evaluation and management.

Dual drug antifungal therapy with amphotericin B and/or posaconazole was given in all diagnosed cases of rhino-orbital-cerebral CAM. Tablet Posaconazole 300 twice daily was given as a loading dose followed by 300 mg once daily for 3 months and intravenous amphotericin B (conventional/lipid complex) was given 3 days preoperatively and 7–15 days postoperatively.

CRP preoperatively was in the range of 2–200 mg/L with a mean of 60 mg/L, whereas 3 months postoperatively, the CRP was in the range of 1–12 mg/L with a mean value of 9 mg/L. Pus discharge was noted in 6% (*n* = 5) patients, and post-operative pain and swelling were present in 7% (*n* = 6) patients and there was wound dehiscence in 11% (*n* = 10) patients [Table 3]. There was mortality in two patients (1.76%) with a known cerebral involvement.

Table 2: Clinical findings, subtypes and pattern

	n (%)
Intra-oral findings	
Mobility of teeth	60 (53)
Pain in teeth	64 (57)
Maxillary mobility	33 (29)
Multiple draining sinuses	35 (31)
Palatal fistula	15 (13)
Exposed bone intra - orally	10 (9)
Nasal, ocular and neurological findings	
Nasal findings	49 (43)
Ocular findings	12 (11)
Neurological findings	2 (2)
Subtypes of rhinocerebral CAM (*n*=113)	
Rhino-maxillary	54 (48)
Rhino-nasal	45 (39)
Rhino-orbital	12 (11)
Rhino-orbito-cerebral	2 (2)
The pattern of osteomyelitis in CAM (*n*=113)	
Lytic	25 (22)
Sclerotic	6 (5)
Mixed	32 (28)
Mixed	50 (44)

CAM: Coronavirus disease 2019-associated MCR

Table 3: Types of surgical management and post-operative complications

	n (%)
Type of surgical management of CAM	
Bilateral maxillectomy	10 (10)
Hemi maxillectomy	5 (5)
Partial maxillectomy	5 (5)
Anteriormaxillectomy	4 (4)
Isolated palatal resection	2 (2)
Zygomatic resection	4 (4)
Sequestrectomy	14 (14)
Maxillary sinus debridement (Caldwell Luc)	14 (14)
Functional endoscopic sinus surgery	41 (41)
Post-operative healing and complications	
Pus discharge	5 (6)
Post-operative pain and swelling	6 (7)
Wound dehiscence	10 (11)

CAM: Coronavirus disease 2019-associated MCR

Discussion

Patients infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) are at high risk for developing fungal infections.[1,2] In this study, 113 patients diagnosed with rhino-orbito-cerebral MCR had a history of COVID-19 infection with 56% of the patients (64 patients) treated in either intensive

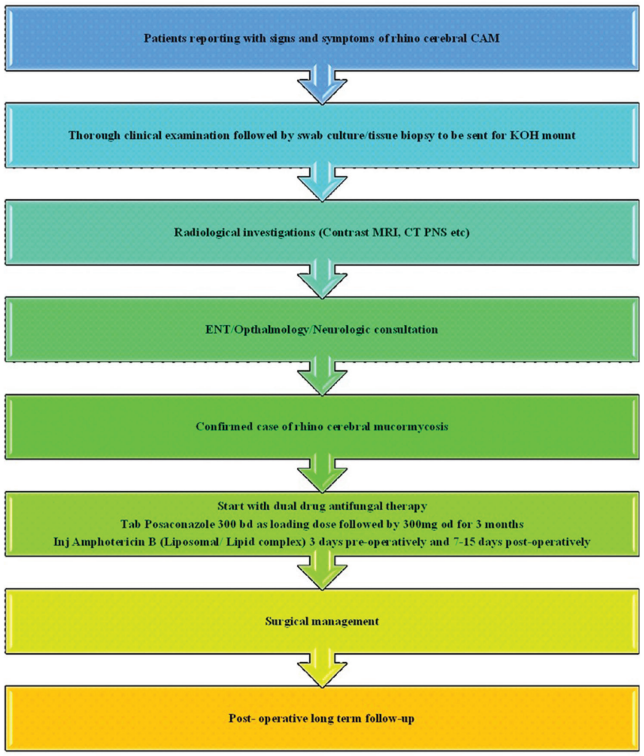

Figure 5: Institute-based protocol for patients reporting with coronavirus disease 2019-associated mucormycosis

care/hospital settings. In this study, 91% of patients had been treated with IV/Oral steroid therapy during their COVID-19 treatment. Although this potential association remains unclear, a strong association between the use of steroids and the development of CAM could be suspected. Immunosuppressive effect of steroids in treating COVID-19 infections usually diminishes after 3–4 weeks Once the immunosuppressant effect reduces, it will kick start the immunity, leading to a decrease in the spread of CAM and limiting the disease in a confined area. Most patients in our study presented with CAM within 2 months of COVID-19 infection, whereas the effects of steroids were still active.

Forty-nine per cent of patients in this study had DM which is a well-known risk factor to develop MCR. The clinical hallmark of MCR is vascular invasion, resulting in thrombosis and tissue infarction/necrosis.[11] Diabetic patients have a higher incidence of microvascular diseases and this along with the delicate architecture of paranasal sinuses leads to more tissue destruction and local dissemination.[12,13] During COVID-19 infection, the inflammatory state induced by hyperglycaemia may be potentiated once the antiviral immunity to SARS-CoV-2 is activated. In addition, Mucorales stimulate the release of proinflammatory cytokines by immune cells. Therefore, MCR associated with COVID-19 might be caused by several divergent inflammatory pathways that contribute to the development of an inflammatory environment conducive to MCR. Most of the patients in our study were male. Roden *et al*. in their review of 929 reported cases of zygomycosis found a higher prevalence of infections in males, but the reasons were unclear. This study also showed a higher percentage of males getting affected with MCR than females.[12] Restrepo *et al*., observed a protective role of oestrogen in paracoccidioidomycosis. However, the protective role of oestrogen in MCR is still not explored.[14]

Regarding clinical findings of CAM, 57% of the patients had intra-oral findings, whereas nasal findings were present in 43% of cases. This finding reflects the list of signs and symptoms that should be 'Red flags' for rhinocerebral MCR by Skiada *et al*. (2021). These were cranial nerve palsy, diplopia, sinus pain, proptosis, periorbital swelling, orbital apex syndrome, ulcers of the palate, maxillary mobility and multiple draining intra-oral sinuses.[15] All patients underwent gadolinium contrast MRI and CT PNS for knowing the extent of bone as well as soft-tissue involvement. CT PNS was extremely helpful in planning the margins for resection of the osteomyelitic bone in this study, whereas MRI had an upper hand in diagnosing early sinonasal involvement.

In this study, fungal culture by KOH mount was used as a diagnostic criterion in pre-operative screening of CAM. All patients received dual drug antifungal therapy 3 days preoperatively and 7–15 days postoperatively (mean = 12 days). Concerning the prognosis, Badiee *et al*. in their study found a significant relationship between MCR and the underlying disease and prior antifungal therapy.[16] Although the mean pre-operative CR*P* values in their study were 57 mg/L, the authors suggested that the role of CRP in the diagnosis of MCR in immunocompromised patients was not clear. In this study, the mean CRP preoperatively 60 mg/L, whereas 3 months postoperatively, the mean CRP was 9 mg/L. This definitive fall in CRP levels (more than 3 times) suggested an improved prognosis in all the patients operated at our centre. Singh *et al*. reported a mortality rate of 30.7% in patients with CAM, whereas Ravani *et al*., in their retrospective study, had a mortality rate of 9.78%.[17,18] All the above studies included other forms of MCR as well, with patients having higher mortality rates in disseminated, gastrointestinal and cerebral involvement. In this study, there were two patients who lost their life secondary to extensive cerebral involvement. Reasons for low mortality were early diagnosis, prompt treatment and inclusion of patients only with CAM of the maxillofacial region.

Conclusions

The conclusions from this cohort emphasise that individuals with severe COVID-19, undergoing corticosteroid therapy and having pre-existing DM are at a significant risk of developing MCR. Early diagnosis, prompt surgical intervention and dual antifungal therapy are crucial in improving the prognosis of these patients.

Limitations of our study are that it is a unicentric observational study and a larger sample size would enhance the data's reliability and facilitate more robust statistical analysis. Multicentre studies are necessary to validate the findings

across diverse settings and populations, to better understand the disease's impact, the risk factors related to CAM and the relationship between COVID-19 and MCR.

Declaration of patient consent

The authors certify that 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, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Baddley JW, Thompson GR 3rd, Chen SC, White PL, Johnson MD, Nguyen MH, *et al.* Coronavirus disease 2019-associated invasive fungal infection. Open Forum Infect Dis 2021;8:ofab510.
2. Bassetti M, Kollef MH, Timsit JF. Bacterial and fungal superinfections in critically ill patients with COVID-19. Intensive Care Med 2020;46:2071-4.
3. Said Ahmed WM, Elsherbini AM, Elsherbiny NM, El-Sherbiny M, Ramzy NI, Arafa AF. Maxillary mucormycosis osteomyelitis in post COVID-19 patients: A series of fourteen cases. Diagnostics (Basel) 2021;11:2050.
4. Kothandaraman N, Rengaraj A, Xue B, Yew WS, Velan SS, Karnani N, *et al.* COVID-19 endocrinopathy with hindsight from SARS. Am J Physiol Endocrinol Metab 2021;320:E139-50.
5. Perricone C, Bartoloni E, Bursi R, Cafaro G, Guidelli GM, Shoenfeld Y, *et al.* COVID-19 as part of the hyperferritinemic syndromes: The role of iron depletion therapy. Immunol Res 2020;68:213-24.
6. Ibrahim AS, Spellberg B, Walsh TJ, Kontoyiannis DP. Pathogenesis of mucormycosis. Clin Infect Dis 2012;54 Suppl 1:S16-22.
7. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, *et al.* Dexamethasone in hospitalized patients with COVID-19. N Engl J Med 2021;384:693-704.
8. Lionakis MS, Kontoyiannis DP. Glucocorticoids and invasive fungal infections. Lancet 2003;362:1828-38.
9. Datarkar AN, Daware S, Gadve V, Pardiwala AF, Pund M, Bhawalkar A, *et al.* Zygomaticomaxillary osteomyelitis due to COVID-19 associated mucormycosis (CAM): A case series of 10 patients. J Maxillofac Oral Surg 2022. p. 1-11. [doi: 10.1007/s12663-022-01809-z].
10. Nagpur Municipal Corporation. Available from: https://nmcnagpur.gov. [Last accessed on 2021 Aug 20].
11. Banerjee I, Robinson J, Asim M, Sathian B, Banerjee I. Mucormycosis and COVID-19 an epidemic in a pandemic? Nepal J Epidemiol 2021;11:1034-9.
12. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, *et al.* Epidemiology and outcome of zygomycosis: A review of 929 reported cases. Clin Infect Dis 2005;41:634-53.
13. Szarpak L, Chirico F, Pruc M, Szarpak L, Dzieciatkowski T, Rafique Z. Mucormycosis-A serious threat in the COVID-19 pandemic? J Infect 2021;83:237-79.
14. Restrepo A, Salazar ME, Cano LE, Stover EP, Feldman D, Stevens DA. Estrogens inhibit mycelium-to-yeast transformation in the fungus *Paracoccidioides brasiliensis*: Implications for resistance of females to paracoccidioidomycosis. Infect Immun 1984;46:346-53.
15. Skiada A, Pagano L, Groll A, Zimmerli S, Dupont B, Lagrou K, *et al.* Zygomycosis in Europe: Analysis of 230 cases accrued by the registry of the European Confederation of Medical Mycology (ECMM) working group on zygomycosis between 2005 and 2007. Clin Microbiol Infect 2011;17:1859-67.
16. Badiee P, Jafarian H, Ghasemi F. Molecular epidemiology of zygomycosis and their related factors in tertiary referral centers in Southern Iran. J Infect Dev Ctries 2020;14:1424-30.
17. 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.
18. Ravani SA, Agrawal GA, Leuva PA, Modi PH, Amin KD. Rise of the phoenix: Mucormycosis in COVID-19 times. Indian J Ophthalmol 2021;69:1563-8.