

Management of COVID-19 associated rhino-orbital mucormycosis and reconstructive options for the resulting extensive defects: a case report

Sujeeth Kumar Shetty, Varun Shukla[^]

Department of Oral & Maxillofacial Surgery, JSS Dental College & Hospital, JSS AHER, Sri Shivarathreeshwara Nagara, Mysuru, India

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Correspondence to: Varun Shukla, MDS. Department of Oral & Maxillofacial Surgery, JSS Dental College & Hospital, JSS AHER, Sri Shivarathreeshwara Nagara, Mysuru 570 015, India. Email: v.shukla095@gmail.com.

Background: With the emergence of coronavirus disease 2019 (COVID-19), fungal co-infections have become increasingly prevalent among critically ill patients, particularly those on prolonged hospital stays or requiring mechanical ventilation. Mucormycosis, an angioinvasive fungal infection, poses a significant challenge in immunosuppressed individuals and those with predisposing factors such as diabetes, with or without ketoacidosis. Rhino-orbital mucormycosis represents the most aggressive and frequently encountered form of this disease, often resulting in extensive surgical resections and debilitating defects. In this report, we present three cases of COVID-19-associated rhino-orbital mucormycosis (CROM), including a unique instance in a non-diabetic patient. Notably, we employed a modified intra-oral approach for surgical interventions, deviating from the commonly practiced extra-oral incisions described in the literature. Additionally, the authors conduct a literature review to explore reconstructive and rehabilitative options for CROM patients, with the ultimate aim of establishing consensus guidelines in this domain.

Case Description: Three patients presented with complaints of unilateral facial swelling, toothache, tooth mobility, and purulent discharge from the right upper posterior tooth region. All patients tested positive for COVID-19, with two of them having a history of type II diabetes mellitus (Cases 1 and 2), while one patient had no known comorbidities. The diagnosis of CROM was confirmed through computed tomography of paranasal sinuses (CT-PNS), magnetic resonance imaging (MRI), direct nasal endoscopy, and biopsy. Aggressive surgical debridement, employing functional endoscopic sinus surgery (FESS) and bilateral maxillectomy, was performed. Treatment included Inj. liposomal amphotericin B (5 mg/kg body weight), followed by posaconazole 300 mg tablets. The patients exhibited favourable tolerance to the procedure, and post-operative follow-up over a period of 6 months demonstrated satisfactory healing.

Conclusions: CROM should be considered even in patients lacking common risk factors. The utilization of an intra-oral approach for surgical debridement, while preserving the palatal mucoperiosteum, offers advantages by reducing complications like nasal regurgitation and crustations within the maxillary cavity, and improved fitting of future prostheses. Despite the availability of various prosthetic and reconstructive strategies for extensive maxillectomy defects, the current approaches predominantly rely on expert opinions rather than established evidence-based recommendations. Therefore, there is an evident need to develop clear consensus guidelines to manage these patients.

Keywords: Coronavirus disease 2019 (COVID-19); mucormycosis; case report; prosthetic rehabilitation; reconstructive surgery

[^] ORCID: 0000-0001-7848-5229.

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Introduction

The outbreak of coronavirus disease 2019 (COVID-19) associated with the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection highlighted that critically ill patients in intensive care units, especially those who required mechanical ventilation or had a longer hospital stay were more likely to develop fungal co-infections (1). Mucormycosis has been reported to be the third most common fungal co-infection after candidiasis and aspergillosis that is caused by opportunistic zygomycete organisms (2). While these fungi are typically harmless in individuals with a healthy immune system, they can pose a severe and challenging infection in patients with immunosuppression or other comorbidities like poorly controlled diabetes mellitus (3). The infection spreads aggressively via the invasion of blood vessels and/or paranasal sinuses (PNS) with subsequent tissue necrosis. It presents as various clinical forms, out of which, the rhino-orbital-cerebral type has been referred to have the most difficult-to-treat progression, ultimately warranting extensive surgical procedures like bilateral maxillectomies (4).

Eventually, they result in large, complex maxillofacial defects with deterioration in the quality of life and long-term impairment, if not reconstructed properly.

Herein we present 3 cases of COVID-19-associated rhino-orbital mucormycosis (CROM), their management, along with the rehabilitative options. Amid the plethora of studies investigating the association between COVID-19 and mucormycosis, most have predominantly focused on patients with diabetes mellitus as a common risk factor (5-8). However, we encountered a unique case of an aggressive form of the disease in a non-diabetic patient with stable blood glucose levels throughout treatment, emphasizing the need to consider this condition in patients bereft of common risk factors. Instead of commonly used extra oral incisions that leave significant scars, we employed an intraoral approach to access challenging areas (9,10). Notably, we achieved favourable outcomes in patients with significantly elevated C-reactive protein (CRP) levels and diabetic ketoacidosis, with no reported morbidity. While existing literature on reconstruction and rehabilitation in CROM patients, primarily comprises isolated case reports and focuses on smaller defects, our objective is to contribute to the development of consensus guidelines for reconstructing and rehabilitating large, debilitating bilateral maxillectomy defects (11-15). We present this article in accordance with the CARE reporting checklist (available at <https://fomm.amegroups.com/article/view/10.21037/fomm-22-66/rc>).

Highlight box

Key findings

- COVID-19 associated mucormycosis can occur in patients without prominent risk factors such as corticosteroid use and diabetes mellitus.
- Effective treatment strategies, including timely diagnosis, correction of underlying defects, aggressive surgical debridement, and prompt antifungal therapy, can reduce mortality rates and improve outcomes in critically ill patients with elevated C-reactive protein (CRP) and blood glucose levels.

What is known and what is new?

- The use of an intra-oral approach for surgical debridement and preservation of palatal mucosa should be considered to prevent complications and improve prosthesis fit.
- Patients with uncontrolled diabetes may develop mucormycosis earlier after COVID-19 diagnosis compared to non-diabetic patients.

What is the implication, and what should change now?

- Further research and evidence-based guidelines are needed for reconstructing and rehabilitating large maxillectomy defects.

Case presentation

Case 1

A 55-year-old female patient admitted to our hospital on 31/05/2021 with a COVID-19 infection complained of swelling on the right side of the face and toothache for the past 10 days. She had a history of uncontrolled type II diabetes. Over the course of her hospitalization, she received 4 mg dexamethasone i.v. twice daily for 10 days. On admission, random blood glucose levels were 246 mg/dL, hemoglobin A1c (HbA1c) 13.2%, total leucocytes count (TLC) 22,000 cells/cu mm, CRP 110.97 mg/L. Urine analysis revealed 1.5% glucose, ketone bodies, and albumin 2+.

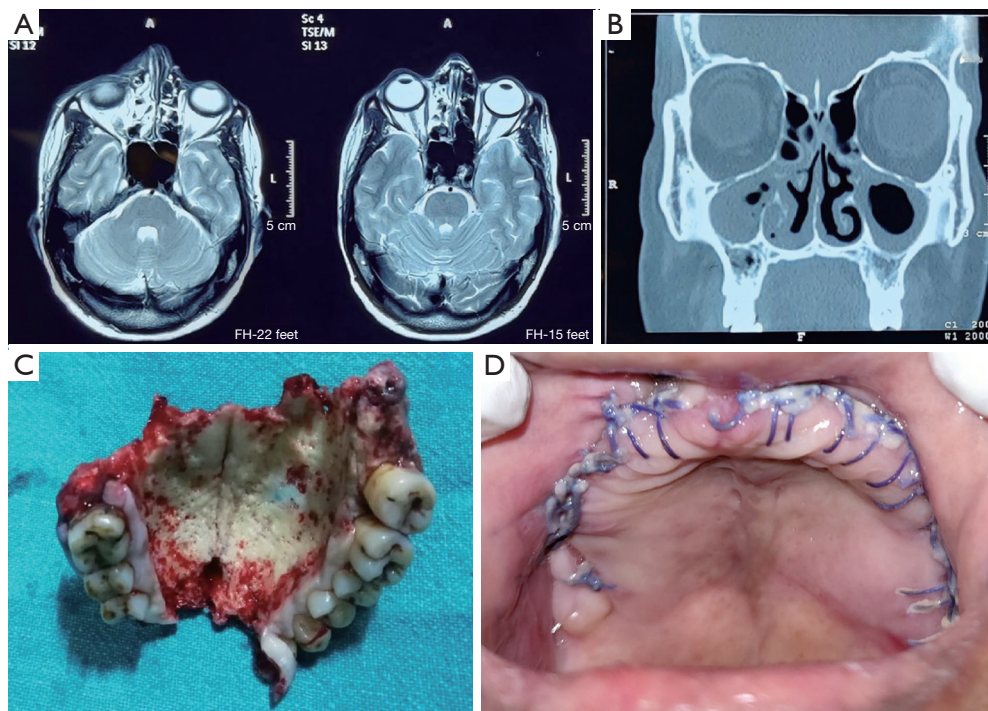


Figure 1 Case characteristics for Case 1 including: (A) axial section of MRI T2 weighted image showing extension of the lesion; (B) CT image; (C) resected surgical specimen; (D) primary closure of the palatal mucosa. MRI, magnetic resonance imaging; CT, computed tomography.

Blood and urine did not show any microbial cultures.

Extra-oral examination revealed swelling over the right middle third of the face extending to the right orbit. The bilateral nasal mucosa appeared pale with nasal septal deviation. Periorbital edema was noted with respect to the right eye. Visual acuity was 6/6 in both eyes with no ophthalmoplegia. Intraoral examination showed mobile maxillary teeth with multiple draining sinuses. The palatal mucosa was tender with a blackish necrotic eschar (*Figure 1*).

Case 2

A 42-year-old male patient presented to us on 11/05/2021 with complaints of swelling over the right side of the face and loosening of teeth for the past 14 days. The patient tested positive for COVID-19 a month back. There were no other existing co-morbidities. Baseline workup showed random glucose (blood) 128 mg/dL, elevated C reactive protein (88.78 mg/dL), increased serum ferritin (808 ng/mL) with reduced levels of blood urea (11 mg/dL), and creatinine (0.62 mg/dL). The blood and urine cultures did not grow any microorganisms. The patient received

dexamethasone 4 mg i.v. and prednisolone 25 mg daily for a period of 7 days. No known comorbidities. Local examination exhibited a firm and tender swelling over the right malar region. Minimal discharge was noted from the right nasal cavity. Intraorally, the patient had missing upper incisors with mobility of all maxillary teeth (*Figure 2*).

Case 3

A 75-year-old male patient with a month-old history of COVID-19 complained of pain and pus discharge from the right upper back tooth region for the past 14 days on 14/06/2021. The patient received a total of 500 mg of i.v. dexamethasone and oral prednisolone combination during his treatment.

The patient had type II diabetes for the past 10 years. Baseline hematological investigations on admission revealed hemoglobin 14.0 g/dL, TLC 14,420 cells/cu mm, HbA1c 12.7%, elevated CRP of 153 mg/L along with hypokalaemia (127 mEq/L). No microbial growth was noted in blood and urine cultures. Examination revealed multiple mobile maxillary teeth with draining sinuses. The ophthalmologic

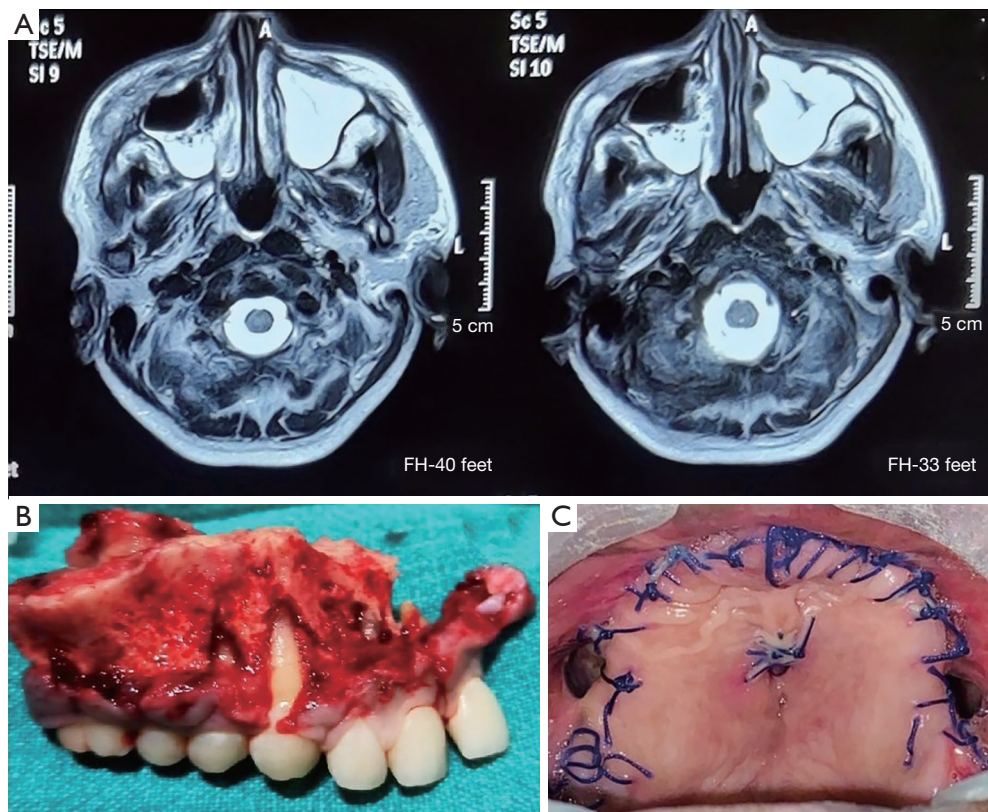


Figure 2 Case characteristics for Case 2 including: (A) axial section of MRI T2 weighted image showing extension; (B) resected maxillary segment; (C) post-op picture at 1 week. MRI, magnetic resonance imaging.

examination was normal (*Figure 3*).

Computed tomography of the paranasal sinuses (CT-PNS) revealed eroded lateral walls of the maxillary sinus with peri-antral fat stranding and thickening of the sphenoidal sinus walls. Direct nasal endoscopy and biopsy were performed.

Magnetic resonance imaging (MRI) brain with orbits and PNS showed diffuse circumferential mucosal thickening of maxillary, ethmoidal and sphenoidal sinuses in all cases.

Liposomal amphotericin B injections of 1.5–5 mg/kg body weight/day were administered to all the patients following a test dose, and the patients were planned for surgical debridement.

Functional endoscopic sinus surgery (FESS) was performed using a modified Denker's approach. Intra-operatively, necrosis of the posterior maxillary sinus mucosa and bony defects in the ethmoidal sinus walls was noted. The excised tissue sent for KOH staining came positive for mucor (*Figure 4*). A bilateral maxillectomy was performed using a per-oral approach and the necrotic tissue was sent

for a frozen section. The histopathological examination revealed fragments of tissue with large areas of necrosis with fungal elements showing broad aseptate hyphae on gram stain suggestive of mucormycosis, hence confirming the diagnosis. A polymerase chain reaction (PCR) test was not performed owing to the patients belonging to the lower income group.

All patients tolerated the procedure well and were discharged after no residual lesion was noted on MRI. The surgical cavity was packed with a bismuth iodoform paraffin paste (BIPP) dressing through nasal antrostomy reducing dead space volume. Patients 1, 2, and 3 received liposomal amphotericin B i.v. in a total dose of 3 g (250 mg/day for 12 days), 2.98 g (270 mg/day for 11 days), and 4.125 g (275 mg daily for 15 days). They were prescribed posaconazole 300 mg orally once daily on discharge and were followed up regularly, showing satisfactory healing (*Figure 5*). No unanticipated or adverse events were observed following the surgical treatment and intervention in this case report. All patients were followed up for a period of 6 months and

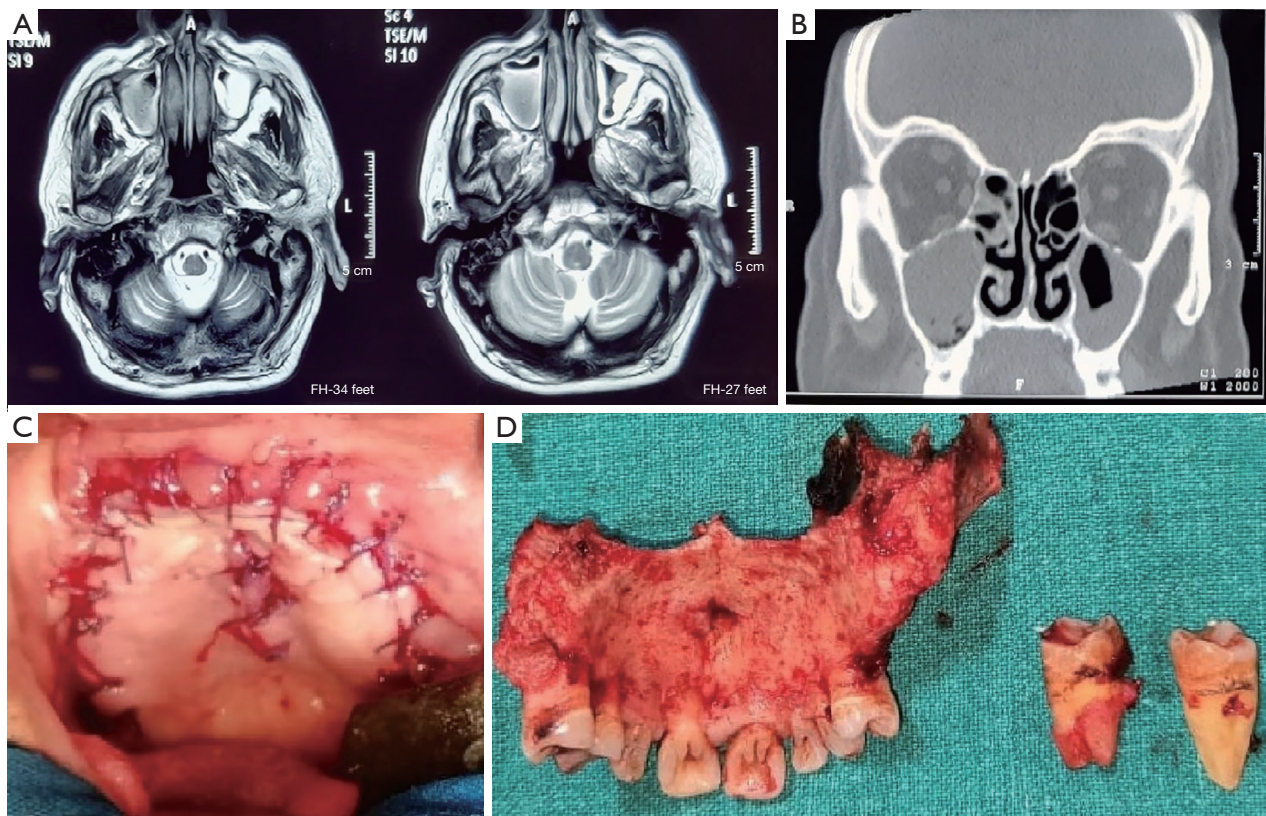


Figure 3 Case characteristics for Case 3 including: (A) axial section of MRI T2 weighted image; (B) CT image of the lesion; (C) closure of mucosa post-resection; (D) resected surgical specimen. MRI, magnetic resonance imaging; CT, computed tomography.

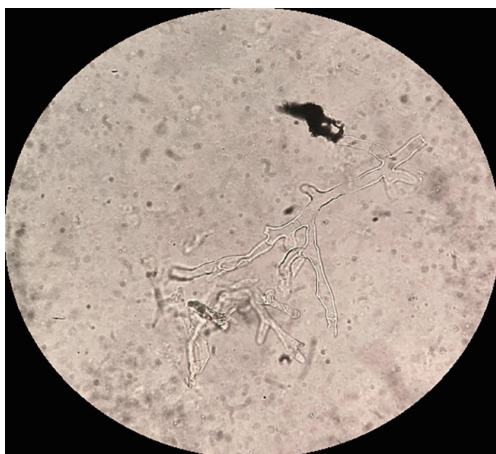


Figure 4 KOH wet mount. KOH wet mount exhibiting the characteristic broad, non-septate, ribbon-like hyphae with wide-angle branching (KOH staining, $\times 40$).

showed satisfactory healing.

The demographic and clinical profiles of the patients have been outlined in *Table 1*.

Immediate feeding plates were fabricated to assist feeding in the interim, as a definite rehabilitation plan was being decided upon.

All procedures performed in this study were in accordance with the ethical standards of the institutional ethical committee of JSS Dental College & Hospital, and with the Helsinki Declaration (as revised in 2013). The authors certify that they have obtained all appropriate patient consent forms. All three patients gave their consent that their images and other clinical information could be used for scientific publication purposes. The patients understand that the names and initials will not be published and due efforts will be made to conceal their identity. A



Figure 5 Post-surgical clinical views for Case 3 exhibiting: (A) extensive intraoral maxillary defect with mobile soft tissue flap 10 days post-surgery; (B) defect showing gradual healing with decreased sloughing and mucous encrustations 4 weeks post-op; (C) completely healed defect with decreased size of communication between oral and nasal cavities at 4 months; (D) extra oral view after prosthetic rehabilitation.

copy of the written consent is available for review by the editorial office of this journal.

Discussion

Rhino cerebral mucormycosis is the commonest clinical form of the infection, accounting for 30–50% of cases, and is fatal, if not treated within a week (16). The spores require a low O_2 environment, high glucose, and iron level, the presence of an acidic medium, and decreased phagocytic activity of white blood cells (WBCs) (17). This makes COVID-19 patients, especially those with diabetic ketoacidosis or concomitant steroid use, ideal hosts.

In a comprehensive review conducted by Dilek *et al.*, analysing 30 publications encompassing a sample size of 100 patients, with 68 patients from India, corticosteroid use (90.5%) and diabetes (79%) emerged as major risk factors

associated with mucormycosis. The mortality rate reported in the analysed cases was 33% (18). It is noteworthy to mention that in our report, none of our patients experienced mortality. Additionally, while factors such as steroid use and diabetes were prevalent in the majority of cases examined, they were not uniformly present in all patients.

Furthermore, the current literature reports that the inflammatory states associated with uncontrolled diabetes, and hyperglycemia potentiated by the antiviral immunity to COVID-19 favours the development of fungal co-infections (19). We found excessive use of corticosteroids to be the common risk factor in the presented cases. All the patients described here received corticosteroids at doses higher than those recommended by World Health Organization (WHO) [6 mg of dexamethasone orally or intravenously or 50 mg hydrocortisone i.v., every 8 hours for 7–10 days in severe or critical COVID-19 (20)]. The authors

Table 1 Demographic data and clinical profiles of the presented cases

Patient	Age/sex	Glycaemic status	COVID-19 history (RT PCR positivity for SARS CoV)	Corticosteroids administered, dose/duration	Haematological parameters	Symptoms pertaining to mucormycosis	CT findings	Surgical management	Antifungal therapy
1	55/F	Uncontrolled type II diabetes (with ketoacidosis)	Yes	4 mg i.v. dexamethasone twice daily for 10 days	Random blood glucose: 246 mg/dL; HbA1c: 13.2%; TLC: 22,000 cells/cu mm; CRP: 110.97 mg/dL; urine glucose: 1.5%; ketone bodies+; albumin 2+	Right sided facial swelling and toothache	Bilaterally eroded lateral maxillary sinus walls with peri antral fat stranding and thickening of sphenoidal sinus walls	Endoscopic sinus debridement and bilateral maxillectomy	3 g liposomal amphotericin B (250 mg/day for 12 days) and 300 mg posaconazole orally
2	42/M	Non-diabetic	Yes	4 mg i.v. dexamethasone twice daily and 25 mg prednisolone daily for 7 days	Random blood glucose: 128 mg/dL; CRP: 88.7 mg/dL; serum ferritin: 808 ng/dL	Right sided facial swelling and generalized loosening of maxillary teeth		Endoscopic sinus debridement and bilateral maxillectomy	2.98 g liposomal amphotericin B (270 mg/day for 11 days) and 300 mg posaconazole orally
3	75/M	H/O type II diabetes (without ketoacidosis)	Yes	A total of 500 mg of i.v. dexamethasone and oral prednisolone over the course of the hospitalization	HbA1c: 12.7%; CRP: 153 mg/dL; TLC: 14,220 cells/cu mm; blood sodium: 127 mEq/L	Pain and persistent pus discharge from the right maxillary dentoalveolar region		Endoscopic sinus debridement and bilateral maxillectomy	4.125 g liposomal amphotericin B (275 mg daily for 15 days) and 300 mg posaconazole orally

COVID-19, coronavirus disease 2019; RT PCR, reverse transcriptase polymerase chain reaction; SARS-CoV, severe acute respiratory syndrome coronavirus; CT, computed tomography; F, female; i.v., intravenous; HbA1c, hemoglobin A1c; TLC, total leucocytes count; CRP, C-reactive protein; M, male; H/O, history of.

also noted that the patients with uncontrolled diabetes (Cases 1 and 3) developed mucormycosis relatively earlier after the diagnosis of COVID-19 as compared to the non-diabetic patient (Case 2).

Available scientific evidence outlines the common clinical features associated with CROM, encompassing symptoms such as headache, periorbital swelling, facial pain and swelling, ophthalmoplegia, proptosis, nasal congestion or discharge, vision impairment, ptosis, dental discomfort or tooth mobility, and palatal discoloration or ulcers (21).

Facial swelling, toothache, nasal congestion, and discharge were consistently observed in all three patients, underscoring the occurrence of these symptoms in CROM cases. Additionally, tooth mobility was noted in one patient, while palatal discoloration or eschar was observed in another. Interestingly, none of the patients reported experiencing headache, vision impairment, or ptosis.

The effective treatment of mucormycosis necessitates:

Prompt diagnosis

The early diagnosis of the disease is paramount in enabling prompt active antifungal therapy. Initiation of amphotericin B therapy within the 5th day of diagnosis has been concomitant with better survival rates. The patients need to be monitored periodically for adverse effects associated with amphotericin B such as nausea, vomiting, rigors, fever, hypertension, skin rash, etc.

Elimination of underlying defects

It is critical to intercept the underlying defects in the host's defence by reducing dosages of corticosteroids and aggressive measures to achieve a euglycemic and normal acid-base status in diabetic ketoacidosis.

Surgical debridement

Thrombosis of vessels with concomitant tissue necrosis prevents the penetration of the antifungals, hence, aggressive surgical debridement is critical for the complete elimination of mucormycosis.

The conventional approach for performing bilateral maxillectomy in such extensive cases involves the use of extra-oral incisions like weber Ferguson or lateral rhinotomy, debriding and resecting the affected bone and adjacent mucosa (9,10).

Wound closure was often problematic, leaving the intraoral

wound open, leading to complications like nasal regurgitation, crustation of the maxillary cavity, and ill-fitting prostheses.

Our modified intra oral approach preserves palatal mucosa after necessary bone resection and debridement, ensuring the periosteum remains attached.

The spared palatal mucosa is sutured with the buccal flap, acting as the fulcrum for prosthesis rotation. As a result, we have incorporated this approach into our surgical management protocol for subsequent patients with rhino-orbital mucormycosis admitted to our hospital.

Rapid antifungal therapy

Liposomal amphotericin B with an initial dosage of 5 mg/kg body weight [10 mg/kg body weight in case of central nervous system (CNS) involvement] is the standard of care (22). Posaconazole has been proven effective in refractory and polyene-resistant mucormycosis. The data supporting combination therapy is limited to support it as a general recommendation (23).

Maxillary reconstruction is a formidable endeavour due to the loss of the central arch, the collapse of the nose, and the loss of orbital support. The current literature regarding successful reconstruction and prosthetic rehabilitation of extensive resection in CROM is limited and primarily consists of isolated case reports (11-15). To address this gap, we aim to provide an overview of the available options after a brief review of the existing literature.

Prosthetic rehabilitation

The placement of an obturator is possible when long zygomatic implants with high-quality zygoma provide anchorage.

Pterygoid implants have had limited use due to technique sensitivity and difficult access.

Reconstruction

Non-vascularized grafts

The coronoid process of the mandible, harvested long enough can be used to provide orbital support in such cases. The natural curvature of the iliac crest and the scapula tip mimics the maxillary alveolar ridge and is sturdy enough to support osseointegrated implants.

Free flaps

Futran *et al.* found reconstruction of maxillectomy defects

using free fibular flaps, reliably implantable, but unable to stabilize an implant-supported prosthesis (24).

The scapula free flap can be used to restore the maxillary arch form while the scapular tip restores the orbital floor. Tailoring the bone to the malar prominence appears to be cumbersome (25).

The iliac crest free flap has been used for such defects restoring the alveolar ridge, zygoma, and infraorbital rim, while the muscle obliterates the sinus and provides oronasal separation (26).

Recent advancements: patient-specific implants (PSIs)

The utilization of pre-fabricated alloplastic implants and autogenous bone grafts is often marred with resorption, infection, and displacement. Recent technological advancements in additive manufacturing and three-dimensional (3D) printing have galvanized reconstructive surgeons towards the use of custom computer-designed PSIs. These provide more accurate defect adaptation, shorter operating times, and more predictable outcomes (27).

The timing of reconstruction is another factor that has been widely discussed, with the majority opinion in favour of delayed rather than immediate reconstruction, giving precedence to clearance of infection (12).

Strengths of the case report include its unique contribution to the existing literature, as it highlights an aggressive form of mucormycosis in a non-diabetic patient with stable blood glucose levels. The use of an intraoral approach instead of extraoral incisions led to favorable outcomes, even in patients with elevated CRP levels and diabetic ketoacidosis, without any reported morbidity. Additionally, the report aims to contribute to the development of consensus guidelines for reconstructing large bilateral maxillectomy defects, which is an area with limited existing literature.

Limitations of the case report include its limited sample size, which precludes making definitive conclusions regarding the age predilection of the disease. Furthermore, the inclusion of unvaccinated patients underscores the need for further studies to explore the potential association between vaccination and the incidence of CROM.

Conclusions

Treatment of mucormycosis includes medical management and aggressive surgical debridement. Although various prosthetic and reconstructive strategies have been presented for the rehabilitation of extensive maxillectomy defects, they

continue to be opinion-based rather than evidence-based. There is a need for multicentric epidemiological studies to understand the true impact of the disease. The importance of combined surgical and prosthetic teams in explaining the options and their outcomes to patients cannot be overemphasized.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <https://fomm.amegroups.com/article/view/10.21037/fomm-22-66/rc>

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <https://fomm.amegroups.com/article/view/10.21037/fomm-22-66/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional ethical committee of JSS Dental College & Hospital, and with the Helsinki Declaration (as revised in 2013). The authors certify that they have obtained all appropriate patient consent forms. All three patients gave their consent that their images and other clinical information could be used for scientific publication purposes. The patients understand that the names and initials will not be published and due efforts will be made to conceal their identity. A copy of the written consent is available for review by the editorial office of this journal.

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