Surgical Challenges in the Management of Post COVID-19 Midface Mucormycosis (PCoMM): An Institutional Protocol

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Background: The coronavirus disease 2019 (COVID-19) pandemic has posed another serious threat, mucormycosis infection, affecting the maxilla and orbitocerebral region. This condition has not spared world population from its merciless claws. This article addresses the challenges faced by the maxillofacial surgeons in setting the protocols from preoperative diagnosis, surgical management to postoperative care, including short-term and long-term rehabilitation. To manage this relentlessly progressing condition, a multispecialty team approach is to be activated in diagnosing, managing, and rehabilitating the patients.

Purpose: The purpose of this clinical study is to document and analyze the clinical and demographic data, presentation of the lesion, the diagnostic methods followed for early clinical detection, and management of post COVID-19 midface mucormycosis. The article also discusses postoperative medical management and prosthetic rehabilitation.

Results: Most of the mucormycosis cases reporting to our center were treated and recovered patients of Severe Acute Respiratory Syndrome Coronavirus 2 infection. Thirty-four (n = 34) case were operated for post COVID-19 midface mucormycosis between October 2020 and December 2021. Male to Female ratio is 1:4.2. The average age of the patients was 57.5 years. Maximum patients were in fifth and sixth decade of life. Maxilla was the involved bone. Treatment was primarily surgical debridement to extended or radical maxillectomy. All patients were treated with Liposomal Amphotericin B and tab posaconazole for 3 to 4 weeks depending upon the age, weight, and physiologic state of the patients to attain an optimal cumulative load. Three patients succumbed to illness postoperatively (n = 3, 1.02%). Average duration of hospital stay was 47 days. The average review period was 5.1 months.

Key Words: COVID-19, liposomal amphotericin B (L-AmB), mucormycosis, posaconazole, SARS-CoV-2

The current Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection is associated with a wide clinical spectrum of coronavirus disease 2019 (COVID-19) that ranges from being asymptomatic to severe disease requiring intensive care unit (ICU) admission. The estimated prevalence of mucormycosis is ~70 times higher in India when compared with the developed world. The rate of admission to ICU is about 5% of all COVID-19 patients. Since the emergence of the COVID-19 pandemic, it has been observed that mucormycosis has caused significant rise in morbidity to infected patients. The most complex, disfiguring and massively involving complication is mucormycosis. The primary most step in the management of mucormycosis is to evaluate the medical condition of diabetes mellites and previous history of steroid therapy. Mucormycosis was diagnosed based on microbiological culture or specific histological features from biopsy specimen collected from patients with clinical symptoms. In addition, computed tomography (CT) and/or magnetic resonance imaging (MRI) of the orbit, brain, and/or paranasal sinuses are of paramount importance in assessing the extent of involvement of mucormycosis affecting the cranio-maxillofacial region. The most common type of mucormycosis is rhino-cerebro-orbital (44%–49%), followed by cutaneous (10%–19%), pulmonary (10%–11%), disseminated (6%–11%), and gastrointestinal (2%–11%). The mainstay of treatment for PCoMM are antifungals and surgical debridement of affected tissues. This study was undertaken to determine the epidemiology, disease characteristics, and outcome of PCoMM reporting to our institution. This prospective study was undertaken with the aim to determine the patient demographics and population at risk, presenting symptoms and signs, the role of comorbidities and medications used to treat COVID-19, and the outcomes of management. The information provided by such a study may help medical professionals to recognize the early clinical features of PCoMM, have a high index of suspicion in the presence of typical symptoms and signs, appropriately triaging patients with possible PCoMM to confirm the diagnosis, establish staging, and initiate early protocol-based multidisciplinary management.

METHODOLOGY

We performed a prospective study of patients with maxillofacial mucormycosis with past history of COVID-19 infection. The study was approved by the Ethics Committee. All patients diagnosed for post COVID-19 maxillofacial mucormycosis were included in the study and were managed between October 2020 and December 2021. A total of 34 patients were treated in the said duration (n = 34). The data base of patients is as given in Supplemental Table 1 (Supplemental Digital Content 1, http://links.lww.com/SCS/E477). The diagnosis of COVID-19 was based on any one of the following: reverse transcription polymerase chain reaction test on nasopharyngeal or oropharyngeal swabs, rapid antigen test, or CT chest scores in the absence of a positive reverse transcription polymerase chain reaction test in a clinically symptomatic case. Patients with symptoms and signs of maxillofacial mucormycosis, in the clinical setting of recently treated COVID-19, were examined for clinical features and...
subjected to diagnostic modalities of nasal endoscopy, mucosal and bony biopsy (from maxillary antrum), contrast-enhanced MRI, or CT scan for the diagnosis of maxillofacial mucormycosis. The simplified form of institutional data card followed is as depicted in Supplemental Table 2 (Supplemental Digital Content 1, http://links.lww.com/SCS/E477). The flowchart for selection and diagnosis of post COVID maxillofacial mucormycosis used in the study is given in Supplemental Table 3 (Supplemental Digital Content 1, http://links.lww.com/SCS/E477).

MANAGEMENT

A thorough clinical examination followed by radiological evaluation and laboratory investigation as enumerated in Supplemental Table 3 (Supplemental Digital Content 1, http://links.lww.com/SCS/E477) were performed in all patients. The figures from Figures 1A–E are described in Supplemental Table 3 (Supplemental Digital Content 1, http://links.lww.com/SCS/E477). Figure 1A depicts potassium hydroxide solution test to identify the Rhizopus spp, Figure 1B depicts Grocott methenamine-silver (GMS) stain to identify the hyphae structures, Figure 1C depicts lactophenol cotton blue preparations (LPCB), Figure 1D depicts sabouraud dextrose agar culture to show expanding mycelial, Figure 1E depicts necrosis of the palatal. After the initial imaging of para nasal sinus view (skull) for screening purpose, all patients were subjected to MR1 (Fig. 2A) and contrast-enhanced CT in case where orbital (Fig. 2B) or cerebral extension was suspected based on clinical evaluation. These images gave the surgical team an insight of 3-dimensional extension of the inflammatory process including the parasanal sinus region (including ethmoids), orbits, frontal and anterior skull base region, intraorbital involvement (ocular muscles, optic neurovascular structures, and intraocular inflammatory deposits), turbinates, and maxillary alveolus. On the basis of the involvement, surgery was planned with the maxillofacial, ophthalmologist, and otolaryngologist (ear, nose, and throat) team. Surgical debridement, depended on the site and extent of involvement, whether to go for local debridement like alveolectomy with preservation of labio-buccal and palatal flaps or to go for radical resection like maxilectomy, turbinectomy, and orbital exenteration. After initial functional endoscopy, with the ear, nose, and throat team (Fig. 2C) to explore the ethmoidal sinuses, radical surgical debridement of the diseased tissue harboring infectious fungal elements, was carried out, to prevent the systemic spread of infection by removal of the nidus. The ophthalmologist team was consulted to rule out orbital spread of infection in clinically and radiologically suspicious cases. Medical opinion was sought to manage the comorbidity like diabetes or chest infection, as well as to monitor the kidney and liver function parameters while on antifungal therapy. Microbiologist and pathologist play key role in diagnosing the PCoMM, as well as ruling out the residual infection during the discharge and recurrence at the time of definitive rehabilitation with patient-specific implants or maxillofacial prosthesis.

Four cases were negative for GMS and potassium hydroxide (KOH) stain. However, they were operated for osteomyelitis maxilla based on the clinical and radiological findings. The resected specimen that was sent for microbiological and pathological evaluation revealed Rhizopus spp and hence included in the study. Local irrigation with AmB or topical hydrogen peroxide were performed on the residual tissues. Iodoform pack allows secondary granulation and removed in 72 hours followed by the irrigation of the wound. In cases with larger necrotic lesions, signifying an aggressive angiinvasive infection and an advanced spread of disease, more aggressive surgical extirpation was done like radical resection with partial or total maxillectomy (Fig. 2D). In cases where, orbital involvement was seen, exenteration was performed (Fig. 2E). Turbinectomy and orbital wall resections were carried out where required.

In case with questionable eye involvement, with preserved vision, transcutaneous retrobulbar Amphotericin injection and 1 mL of 3.5 mg/mL Amphotericin for 3 days was administered. This was also be given in patients who underwent sinus debridement where the orbital wall was breached. Orbital debridement was done where breach of medial wall was present. In disease beyond medial orbit with proptosis and intracranial space involvement exenteration was done.

Custom-made acrylic split was sutured to the margins of the surgical defect to protect the postresection wound, to hold the medicated roller gauze insitu and to aid in early resumption of oral intake by the patient. All resected margins were sent for histopathological evaluation for final confirmatory diagnosis (Fig. 2F). Postoperatively, patients with a respiratory rate of >12/min, tidal volume of >5 mL/kg, SpO₂ >95%, and following verbal commands are extubated before shifting to postoperative ward. Hemodynamically unstable patients, with no or minimal respiratory effort, were shifted to ICU in an intubated state. Postoperatively, renal, electrolyte, coagulopathic, hemodynamic, and respiratory monitoring were done.

The first-line drug of choice for the treatment of PCoMM was Liposomal-Amphotericin B (L-AmB) (5 mg/kg/d). The single most important issue in managing a patient with mucormycosis is appropriate blood glucose control. This was meticulously followed in all our patients. Glycated Hemoglobin test (HbA1C) during admission and fortnightly monitoring of blood glucose level was done. Diabetic ketoacidosis was managed with insulin therapy and concomitant use of sodium bicarbonate. Thrombolytic therapy with prophylactic dose (1 IU/kg body weight) of enoxaparin or equivalent of LMWH was used with caution in those patients had/have deranged coagulation parameters. Postoperatively patient was kept on L-AmB (5 mg/kg/d) until a cumulative dose of 2.5 to 3 g was reached. Early step-down therapy to Posaconazole (after 4–6 wk of AmB) was followed (Syrup, Intravenous, or Oral 200 mg twice daily). Renal function test was performed weekly to monitor urea, creatinine, and GFR values. All patients were subjected for postoperative contrast-enhanced CT after 4 to 6 weeks to confirm the disease-free state radiographically. Patients were discharged between 8th and 12th week after surgery. All patients were reviewed at 1-week intervals for 1 month followed by 2-week interval for 1 month followed by monthly review thereafter. The acrylic splint was regularly cleaned and resecured. After at least 8 weeks of clinic-radiological disease-free state, the patients were referred for fabrication of surgical obturator. None of our cases have entered into the timescale of reconstruction or definitive prosthetic rehabilitation.

RESULTS

This prospective study was conducted on 34 patients with PCoMM. The study included 19 male patients (n=19) and 15 female patients (n=15) (Fig. 3A). The average age distribution was 57.5 years (Fig. 3B). Maximum patients were between 51 and 60 years of age (n=15) followed by 61 to 70 years (n=10). Twenty-one patients (n=21) had steroidal therapy as one of the modes of COVID managements and 15 patients required oxygen supplementation in the management. Of 34 patients, included in the study, 17 patients had both steroid and oxygen therapy and 06
patients had no documented history of oxygen and steroid therapy (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/SCS/E477). Of 34 patients, 30 patients were proven positive for KOH in the tissue sample sent from affected region of the oral cavity showing Rhizopus spp with right angle branching and ribbon-like folding. Nineteen patients were positive for GSM stain, demonstrating the fungal hyphae. The primary mode to determine the extent of the disease and involvement of orbit, antrum,
FIGURE 2. (A) Sagittal magnetic resonance imaging showing retrobulbar inflammatory deposit. (B) Axial computed tomography depicting osteolysis of maxilla and alveolar. (C) Functional endoscopy of ethmoid region. (D) Resected maxilla with alveolus and palate. (E) Orbital exenteration and hemostasis at superior orbital fissure and orbital. (F) Hyphal entrapment in necrotic tissue, angioinvasion, neutrophilic soft tissue infiltrate, or granuloma with histiocytic giant cells (×10).
ethmoids, and cranial cavity was CT. Patients were treated for complete resection of the disease with reasonable encroachment to the vicinity of vital structures like orbital contents, ethmoid sinuses, sphenoid sinuses, and skull base. In 19 cases, functional endoscope was performed to explore the ethmoids and maxillary antrum to collect biopsy sample and to enucleate the diseased structures so as to decrease the viral load. The primary surgery remained resection through total Xmaxillectomy ($n = 12$), hemi-maxillectomy ($n = 5$), subtotal maxillectomy ($n = 8$), or extended maxillectomy ($n = 9$) (Fig. 3C). In 4 cases, orbital exenteration ($n = 4$) is done where MRI images showed retrobulbar extension of the lesion or involvement of the orbital wall from the oroantral extension. Inferior turbinectomy was done based on the involvement and preservation of the palatal flaps was also based on the intactness of the tissue, free from fungal necrosis. The average loading dose of L-AmB was 2.5 to 3 g. Average duration of hospital stay was 47 days. Twenty patients ($n = 29$) were placed on Posaconazole therapy 400 mg 12 hourly for 14 days post discharge for complete fungal-free state. The average duration of follow-up was 5.1 months. The most common complication was wound dehiscence ($n = 9$), followed by local infection ($n = 3$) and stitch abscess ($n = 2$). Total mortality was 3. Out of which, 2 patients who had cerebral extension expired during postoperative hospital care. One patient expired because of multiple organ dysfunction syndrome and eventually cardiopulmonary arrest. All patients were subjected for postoperative histopathological examination to rule out the residual disease.

**DISCUSSION**

**Incidence and Prevalence**

The occurrence of mucormycosis, a rare disease, in the general population was previously cited as 0.005 to 1.7 per million population. However, the incidence of mucormycosis in India was reported to be 0.14/1000 in diabetic patients, which is higher than that reported in other parts of the world. India is the diabetic capital of the world with almost 62 million patients. This led to mucormycosis being a major public health burden during this COVID-19 pandemic phase. In 1 study, diabetes mellitus (DM) was the underlying disease in 72% of mucormycosis cases. In reported cases, 8% to 22% presented with diabetic ketoacidosis, who developed mucormycosis. In addition, there had been geographic difference in the rate of DM among patients with mucormycosis in India. The prevalence of DM was a major risk factor with regional differences ranging from 67% in North India to 22% among patients from the South of India. Underlying comorbidity, particularly, diabetic mellitus and injudicious administration of corticosteroids are considered to be probable

![Figure 3](https://example.com/figure3.png)

**FIGURE 3.** (A) Gender distribution. (B) Age distribution. (C) Maxillectomy procedures done. (D) Contributing factors of post COVID-19 mucormycosis. COVID-19 indicates coronavirus disease 19.
causes for post-COVID mucormycosis, further complicating the pandemic scenario.

**Risk Factors**

There are multiple possible contributing factors for the development of mucormycosis among patients with COVID-19 and these include DM, obesity, use of corticosteroid, and the development of cytokine storms (Fig. 3D). The triad of SARS-CoV-2, steroid, and uncontrolled DM have contributed toward a significant increase in the incidence of angioinvasive maxillofacial mucormycosis. In recent studies, the susceptibility to mucormycosis with diabetic ketoacidosis is associated to serum iron dissociated from transferrin. The iron liberated gets transported into the fungus by the high-affinity iron permease. The presence of peripheral microthrombi is also associated with the unexplained increase of mucor cases in India post second wave; however, further correlating research works are required in the field.

Other than the host-related factors that could have possibly led to a surge in the number of mucormycosis infection patients in the current pandemic, there are other factors that can also lead to this fungal infection. The factors are enlisted below: 17,18

1. Dirty linen, contaminated linen shelves, and dirty bins
2. Contaminated air handling units and ventilation ducts
3. Negative pressure isolation rooms
4. Water leak (wall dampness leading to accumulation of fungus)
5. Hospital construction; dust and moisture
6. Fungal contamination of nebulizer devices.

D’Amico and colleagues have stated ways to prevent corona virus prevention in dental clinic setup. The authors have stated that following the guidelines and the strictest protocols for the disinfection of operators and environments will effectively prevent the transmission of the virus and thereby the complications. 19

Mucormycosis is an opportunistic, potentially lethal, angioinvasive fungal infection predisposed by uncontrolled DM, corticosteroids, immunosuppressive therapy, primary or secondary immunodeficiency, hematological malignancies, hematological stem cell transplantation, solid organ malignancies, solid organ transplantation, and iron overload. 20 In this study, 24 patients had history of DM (n=24, 80%) and 18 patients had steroidal therapy during the treatment phase of COVID-19 infection (n=18, 60%). Other less common risk factors include intravenous drug use, human immunodeficiency virus infection, renal failure, liver diseases, and chronic alcoholism, and malnutrition and low birth weight in the pediatric population. Postpulmonary tuberculosis and chronic kidney disease have been found to be emerging risk factors based on studies in the Indian population. 13

It can affect the nose, sinus, orbit, central nervous system, lung, gastrointestinal tract, skin, jaw bones, heart, kidney, and maxillar sinus. In our study, out of 35 patients, 18 patients (n=18, 53%) are from farming background. Farmers those use organic manure are more prone to this disease, as organic manure often contains animal excreta and decayed substance, which has high concentration of Mucorales. 21 This finding is evident in our study. Mucormycosis of midface with orbital and cranial involvement is the most common presentation, contributing to about two thirds of all cases of mucormycosis. 22 In this study, oro-antral involvement was the maximum followed by orbitalantral and orbitoethmoidal with cerebral involvement.

**Diagnosis and Surgical Management**

The first step in diagnosing PCoMM is to conduct a diagnostic nasal endoscopy and obtain nasal tissue or nasal scrapings from the affected area. 23 Tissue biopsies constitute the best specimen for the diagnosis of mucormycosis. If a biopsy is not possible, nasal scrapping and nasal swabs should be used for direct examination; though nasal swab and discharges are unreliable as the yield is low in microscopy and cultures. In case of sinusitis, sinus biopsies must be taken. Direct microscopy of clinical specimens, allows a early diagnosis of mucormycosis in 10% to 20% KOH in the laboratory. 24 Culture identification is done either by conventional methods such as slide culture or lactophenol cotton blue preparations or by Matrix-Assisted Laser Desorption/Ionization-Time of Flight. 25 It is strongly recommended that Ziehl-Neelsen or Acid-Fast Stain be done in all cases as antifungal susceptibility profiles differ between species and patients reporting with PCoMM have multiple comorbidities. It is therefore mandatory to rule out Mycobacterium sp (Acid-Fast). In our study, all patients were subjected for KOH mount, culture growth and GMS stain for screening and final diagnosis. The histopathological evaluation of the resected specimen was done for all patients.

The extent of the disease decides the mode of surgery. To detect and plan the disease involvement and resection cuts, CT is the gold standard imaging modality. To evaluate the orbital spread of cerebral involvement, MRI in the adjunct modality. All cases are subjected for CT scan and MRI, where required. Perineural invasion is another distinctive feature of rhino-orbito cerebral mucormycosis (ROCM). 26 This along with angioinvasion accounts for early optic nerve involvement and orbital apex syndrome. 16 In this respect, decision of orbital exenteration is often controversial and there is no standard guideline regarding decision-making of orbital exenteration in rhino-orbital cerebral mucormycosis patients. 27 The extent of the disease, affecting, alveolus with or without palatal involvement, orbits with or without apex involvement, pterygopalatine fossa determine the nature of resection. In our study, the surgical resection ranged from alveolectomy and curettage to radical and extended maxillectomy with exenteration. These details are depicted in Supplemental Table 4, Supplemental Digital Content 1, http://links.lww.com/SCS/E477 and Figure 3C. The upper respiratory anatomy is compromised notably in patients who undergo surgical resection of sinomaxillary region. This is due to initial phase of postsurgical edema and loss of vital anatomical structures in the upper pharyngeal airway. Therefore, need arises to maintain adequate oxygen saturation through assisted airway. Cavallo and colleagues in their technical note have postulated for producing connectors with breathing devises with the aid of Computer-Aided Design/Computer-Aided Manufacturing. They developed respiratory device with the application of two 3-dimensional printed plastic valves “Charlotte” and “Dave” to the easybreath mask. 28

The resection plan and the modes to reconstruct the residual defects after reasonable period of disease-free state should go hand in hand. In our study, we waited for a period of 4 to 6 months in follow-up so as to attain a disease-free period and definitive surgical obturators. Soft tissue and hard tissue reconstruction of the defect sites using autologous-free or pedicled grafts or patient-specific implants can be planned subsequently.

**CONCLUSIONS**

Early diagnosis and management of PCoMM has tremendous influence on the outcome of the treatment. Treating the underlying comorbidities, especially DM is key to the management protocol. Early sign of suspicion should be thoroughly evaluated clinically and radiologically to formulate the resection plan. Amphotericin B should be started in the early course of the disease. Critical areas like orbit or cerebral extension should
be managed with multispecialty team. Constant follow-up and optimal time to start the reconstructive management depend upon a disease-free state of atleast 4 months.

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Tissue Expander Followed by Autogenous Bone Graft Versus Autogenous Bone Graft Alone for Mandibular Reconstruction: Quantitative Assessment

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Background: The use of a tissue expander in maxillofacial intraoral tissue reconstruction is a developing approach, which provide adequate tissue coverage and aesthetics.

Objectives: The purpose of this study was to quantitatively compare the use of a soft tissue expander in conjunction with

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Received March 14, 2022.
Accepted for publication July 30, 2022.
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The authors report no conflicts of interest.

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal’s website, www.jcraniofacialsurgery.com.

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ISSN: 1049-2275
DOI: 10.1097/SCS.0000000000008979

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