



POST-COVID-19 MUCORMYCOSIS: A CROSS-SECTIONAL STUDY AT A GOVERNMENT MEDICAL COLLEGE HOSPITAL IN CENTRAL REGION OF INDIA

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Abstract

Background: The surge in cases of COVID-19 in India during the second wave of the pandemic was associated with increased reporting of invasive mucormycosis. The most common type was rhino-orbito-cerebral mucormycosis, with many cases showing involvement of palate and maxilla. Management included antifungal therapy and aggressive surgical debridement, with maxillectomy performed in many patients.

Materials and Methods: A cross-sectional analytical study was performed in department of Dentistry at a Government Medical College Hospital in central region of India. A total of 108 cases of post-COVID-19 mucormycosis were included in the study. Complete case history including the treatment received for COVID-19, presence of any co-morbidity, imaging findings and histopathological findings were recorded. Presence of oral findings pertinent to mucormycosis were recorded. Data was collected regarding treatment received by the patients.

Results: 77 (71.3%) patients were males and 31 (28.7%) patients were females. 79 (73.1%) patients had Diabetes mellitus as co-morbidity. 69 (63.9%) patients received inhalational oxygen therapy, 82 (75.9%) patients received injection steroid and 52 (48.1%) patients received injection remdesivir. 71 (65.7%) patients showed presence of oral manifestations of mucormycosis. 33 (30.6%) patients had multiple draining sinuses over periodontium, 51 (47.2%) patients had swelling/ulcer/black eschar/bone exposure over palate or maxillary/mandibular bone and 59 (54.6%) patients showed pain/mobility/tenderness of teeth. All the patients received systemic anti-fungal therapy. Functional endoscopic sinus surgery (FESS) was performed in 105 patients. 55 patients underwent maxillectomy and two patients underwent endoscopic maxillectomy. Three patients underwent marginal mandibulectomy. Prosthetic obturator with complete/partial denture was fabricated for 14 patients.

Keywords: COVID-19, mucormycosis, Diabetes mellitus, maxillectomy, obturator

Introduction

The infection of COVID-19 emerged in 2019 and was declared a global pandemic in March 2020 by WHO.¹ The world witnessed several waves of this pandemic. The clinical presentation of the disease in all these waves remained more or less similar, with differences in the severity of infection, the second wave that peaked in India in April-May 2021, being the most severe.² Due to the increased severity of symptoms in the second wave, there was a rise in the usage of systemic steroids to suppress inflammation. Excessive use of steroids led to the emergence of opportunistic infections, the most prominent of which was rhino-orbital-cerebral mucormycosis (ROCM). Invasive mucormycosis is a life-threatening fungal infection that most frequently occurs in patients with underlying co-morbidities impacting immune system function.³

Mucormycosis is an angio-invasive infection caused by the ubiquitous filamentous fungi of the Mucorales order of the class of Zygomycetes.⁴ Mucorales are thermotolerant molds that are supposedly ubiquitous in nature and widely found on organic substrates, including bread, decaying fruits, vegetable matter, crop debris, soil between growing seasons, compost piles, and animal excreta.⁵ The major route of infection is via inhalation of spores, which then spread to involve the paranasal sinuses and lungs.⁶ The fungal spores can grow hyphae in paranasal sinuses and can further extend, through anatomical connections, to the orbit, brain and maxillary alveolus, periodontal tissues and palate.⁷

Individuals with mucormycosis can have diverse clinical manifestations contingent on the immune status of the host, the extent of the infection, and the involved organs. Invasive mucormycosis has been categorized into six distinct clinical syndromes based on infection: pulmonary, rhino-orbital, cutaneous, gastrointestinal and disseminated mucormycosis, and a miscellaneous form involving the bones, breasts, kidneys etc. Rhino-orbital syndrome is the most prevalent manifestation of mucormycosis, followed by pulmonary, cutaneous, and disseminated disorders. Gastrointestinal tract and renal mucormycosis are very rare.⁸ Rhino-orbital-cerebral mucormycosis (ROCM) is the most frequent presentation among patients with Diabetes mellitus and hyperglycemia, particularly with ketoacidosis, while immunocompromised patients (including those with hematological malignancies and transplant recipients) frequently present with pulmonary involvement and disseminated infection.⁹

Patients with ROCM present with symptoms that are consistent with acute sinusitis such as fever, headache, sinus pain, and nasal congestion. In vulnerable hosts, however, progression of the infection with invasion of the orbit and palate and further extension to the brain may occur. This can result in a number of significant clinical abnormalities including intra-oral abscess with draining sinuses over periodontium, mobility/pain of teeth, formation of black eschar/bone exposure over palate, ophthalmoplegia, vision loss, cranial neuropathies, and changes in mental status.¹⁰

In the present study, we collected and analysed data of post-COVID-19 mucormycosis patients who attended department of Dentistry at Government Medical College and Hospital in central region of India.

Aim: To collect and analyse data on management of COVID-19 infection, oral findings, imaging findings, histopathological findings and treatment strategy of post-COVID-19 mucormycosis patients.

Materials and Methods

Study setting: The study was performed in the department of Dentistry at a Government Medical College and Hospital in central India.

Study duration: May–June 2021.

Study design: A cross-sectional analytical study.

Inclusion criteria:

1. Patients with clinical features/proven diagnosis of mucormycosis with a recent history of COVID-19 infection.

Exclusion criteria:

1. Patients infected with COVID-19 without features of mucormycosis.
2. Those patients who did not give consent for participating in the study.

Sampling method and sample size: The convenience sampling method was used, and 108 patients of post COVID-19 mucormycosis who visited department of Dentistry were included in the study.

Data collection: Complete case history including the demographic data, COVID-19 status, signs and symptoms, treatment received during the course of hospitalization for COVID-19 was collected through a questionnaire. Presence or absence of Diabetes mellitus or any other co-morbidity was recorded. For each patient data was collected whether they received inhalational oxygen therapy, systemic glucocorticoids and injection remdesivir for management of COVID-19 infection. Detailed clinical examination of patients was conducted and presence or absence of oral manifestations pertinent to mucormycosis was noted. These included presence of multiple draining sinuses over periodontium, pain/mobility/tenderness of teeth and swelling/ulcer/black eschar/bone exposure over palate or maxillary/manbicular bone.

Findings of computed tomography of paranasal sinuses (CT PNS) for all the patients and magnetic resonance imaging of paranasal sinuses (MRI PNS), wherever applicable were noted. Findings of KOH mount staining, histopathological examination and/or fungal culture reports were recorded.

The treatment strategy of mucormycosis included a multidisciplinary team approach with the administration of intravenous and oral antifungal drugs as well as surgical debridement of necrotic tissue. Data was collected regarding anti-fungal and surgical treatment received by the patients. Surgical procedures included Functional Endoscopy Sinus Surgery (FESS), maxillectomy, mandibulectomy,orbital decompression or exenteration.

Data analysis: The collected data was analyzed using SPSS software. Chi square test was applied to check whether there was any association between oral manifestations of mucormycosis with various study variables.

Informed consent: All the patients included in the study signed an informed written consent to participate in the study.

Results

Age and sex (Table 1): The study included a total of 108 patients. The age range of the patients was 21 to 83 years. Out of the total patients, 77 were males and 31 were females.

Table 1: Distribution of study participants according demographic variables

Demographic variable		
Age	Mean	50.9 years
	Standard Deviation	12.9 years
Sex	Male	77 (71.3%)
	Female	31 (28.7%)

Co-morbidity (Table 2): Out of the total patients, 79 patients had Diabetes mellitus as co-morbidity. One patient had chronic kidney disease as co-morbidity. Rest co-morbidities included one case of mitral valve replacement, one case of ischaemic heart disease and a single case of seizure disorder.

Table 2: Frequency distribution of study participants according to mucormycosis data

Variable		Frequency	Percentage
History of COVID-19	Present	89	82.4
	Absent	19	17.6
Diabetes mellitus	Present	79	73.1
	Absent	29	26.9
History of Hospitalization for COVID-19	Present	85	78.7
	Absent	23	21.3

COVID-19 infection and its management: 89 patients had documented history of COVID-19 infection during the second wave of the pandemic. Out of these 85 patients had a history of hospitalization for the management of COVID-19 infection (Table 2). Amongst these, 69 patients received inhalational oxygen therapy, 82 patients received injection steroid and 52 patients had received injection remdesivir during treatment for COVID-19 (Table 3). 19 patients had no documented history of COVID-19 infection in the second wave and these were the individuals who had not received oxygen therapy, steroidal treatment and injection remdesivir before suffering from mucormycosis.

Table 3: Distribution of study participants according to history of treatment received for COVID-19

H/O Treatment Received		Frequency	Percentage
Injection Steroids	Present	82	75.9
	Absent	26	24.1
Injection Remdesivir	Present	52	48.1
	Absent	56	51.9
O ₂ Therapy	Present	69	63.9
	Absent	39	36.1

Oral findings (Table 4): Out of the total patients, 71 patients showed presence of oral manifestations due to involvement of oral tissues by mucormycosis. 33 patients had multiple draining sinuses over periodontium (Figure 1), 51 patients had swelling/ulcer/black eschar/bone exposure over palate (Figure 2) or maxillary/mandibular bone and 59 patients showed pain/mobility/tenderness of teeth.

Table 4: Frequency distribution of study participants according to oral manifestations

Oral manifestation		Frequency	Percentage
Abscess over periodontium	Present	33	30.6
	Absent	75	69.4
Pain/mobility of teeth	Present	59	54.6
	Absent	49	45.4
Swelling/ulcer/black eschar/bone exposure	Present	51	47.2
	Absent	57	52.8



Figure 1: Multiple draining sinuses over maxillary gingiva



Figure 2: Ulceration with bone exposure over palate

CT/MRI PNS findings: CT/MRI study of 105 patients showed findings suggestive of fungal sinusitis and three patients showed features of mandibular osteomyelitis.

Histopathological examination: KOH mount staining, histopathological examination and/or fungal culture were positive for presence of mucormycosis. Hematoxylin and eosin stained histopathological sections showed broad aseptate fungal hyphae with irregular branching usually at 90° angle (Figure 3). Special stained (PAS reaction) section showed presence of magenta coloured fungal hyphae along with sporangia containing spores (Figure 4). KOH mount of one patient showed presence of septate hyphae and histopathological examination of one patient demonstrated presence of septate hyphae, suggestive of Aspergillosis.

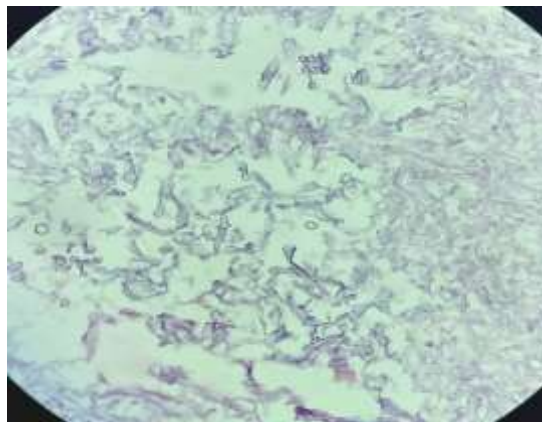


Figure 3: H & E stained section shows broad, aseptate (or pauciseptate) fungal hyphae with irregular branching usually at 90° angle

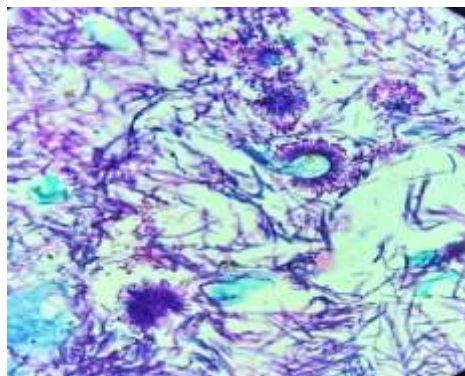


Figure 4: Special stain (PAS reaction) shows magenta coloured fungal hyphae along with sporangia containing spores

Treatment: All the patients received systemic anti-fungal therapy. The average number of days of administration of liposomal Amphotericin B included 14 days followed by oral posaconazole for 14 days. Functional endoscopic sinus surgery (FESS) was performed in 105 patients. 55 patients underwent open partial/subtotal/total maxillectomy (Figure 5, 6) and two patients underwent endoscopic maxillectomy using modified Denker’s approach. Three patients underwent marginal mandibulectomy (Figure 7). Thus, a total of 60 patients were treated by maxillectomy or mandibulectomy (Table 5). Two patients were treated by Caldwell Luc operation. Orbital decompression was performed in 2 patients and 8 patients underwent orbital exenteration. After discharge the patients were kept on regular follow-up for six months (Figure 8). After complete healing in patients treated with maxillectomy, prosthetic obturator with complete/partial denture was fabricated for 14 patients in the department of Dentistry of our hospital (Figure 9).

Table 5: Frequency distribution of study participants according to the treatment received

Treatment received		Frequency	Percentage
FESS	Given	105	97.2
	Not Given	3	2.8
Maxillectomy/Mandibulectomy	Given	60	55.6
	Not Given	48	44.4



Figure 5: Intraoperative picture of patient undergoing maxillectomy



Figure 6: Excised specimen of maxillectomy



Figure 7: Excised specimen of partial mandibulectomy



Figure 8: Post-operative follow-up showing bilateral oro-antral communication after healing of maxillectomy wound



Figure 9: Obturator complete denture fabricated for the patient shown in figure 8

Association of oral manifestations of mucormycosis with various variables (Table 6): There was no statistically significant association between history of hospitalization, history of treatment received, and patients requiring FESS with oral manifestations of mucormycosis.

Table 6: Association of oral manifestations of mucormycosis with various variables

Variable	Abscess (P value)	Pain/mobility of teeth (P value)	Palatal swelling (P value)
H/O Hospitalisation	0.301	0.46	0.94
O ₂ Therapy	0.63	0.27	0.81

Injection steroid	0.15	0.31	0.9
Injection Remdesivir	0.64	0.81	0.18
FESS	0.91	0.67	0.63
Maxillectomy/Mandibulectomy	0.0001	0.0001	0.0001

P value < 0.05 is statistically significant

Among 33 patients with abscess, 31 had undergone maxillectomy. Among 59 patients with pain/mobility of teeth, 50 had undergone maxillectomy. Among 51 patients with swelling/ulcer/black eschar/bone exposure over palate or maxillary/mandibular bone, 45 had undergone maxillectomy. There was a statistically significant association between each oral manifestation of mucormycosis (presence of abscess, pain/mobility of teeth, swelling/ulcer/black eschar/bone exposure) and patients requiring maxillectomy/mandibulectomy.

Discussion

Mucormycosis is a rare but serious angio-invasive infection caused by a group of fungi called mucormycetes. Spores of these ubiquitous fungi can be inhaled and then infect the lungs and sinuses and extend into the brain and eyes.¹¹ The Mucorales have a unique capability of angio-invasion causing vasculitis and thrombosis of vessels, resulting in subsequent tissue necrosis.¹² Many patients demonstrate oral manifestations due to extension of disease from maxillary sinus to the palate and maxillary alveolus.^{13,14} Post-COVID-19 mucormycosis involving mandible has also been reported.¹⁵ The symptoms associated with ROCM are of varying degree ranging from runny nose, unilateral or bilateral facial swelling, orofacial pain, low to high grade fever, headache, blurred vision due to proptosis and involvement of orbital contents to loosening of teeth, destruction of periodontal tissue and appearance of black necrotic eschar or dead bone in the palate, buccal vestibule or the maxillary alveolus along with formation of oro-nasal/oro-antral communication. Although, in the orofacial and maxillofacial region mucormycosis is very rare especially in healthy, immune competent individuals but immune compromised are quite vulnerable to these opportunistic infections which can involve soft and hard tissues of the facial skeleton necessitating surgical intervention along with high-dose, long-term parenteral antifungal therapy.¹⁶ Poor drug penetration in the necrosed and de-vitalised tissue mandates the need for surgical debridement.

In the present study 108 patients who suffered from post-COVID-19 mucormycosis were included. 71.3% of patients were male and 28.7% of patients were female. Similar findings were observed by Pathak et al. and Somkuwar S et al. who found more involvement of males (60.9% and 71% respectively) as compared to females (39.1% and 29% respectively).^{14,17} Aranjani et al. as well as Satish et al. also had similar findings.^{18,19} Whereas Manda et al. found more involvement of female patients (76.5%) as compared to male (23.5%) patients.²⁰ A study on murines found that estrogen has been shown to stimulate pro-inflammatory cytokines (e.g., IL-12, IFN- γ and TNF- α), and down-regulate IL-10. In contrast, the synthesis of IL-10 may be enhanced by testosterone. Thus it was found that female mice were more resistant to mucormycosis as compared to male mice.²¹

In our study 73.15% of patients had Diabetes mellitus as co-morbidity. Similarly, Pathak et al. found that 73.9% patients had Diabetes as a risk factor.¹⁷ Prakash et al., in a nationwide multi-center study of 388 confirmed or suspected cases of mucormycosis in India prior to COVID-19, found that 18% had diabetic ketoacidosis and 57% of patients had uncontrolled Diabetes mellitus.²² Singh et al. in case series of 101 mucormycosis cases in Covid-19 patients, found that 80% cases had Diabetes mellitus.²³ In asystematic review conducted by John et al. that reported the findings of 41 confirmed mucormycosis cases in people with COVID-19, Diabetes mellitus was present in 93% of cases.²⁴ Bala K et al. found that presence of Diabetes mellitus significantly increases the odds of contracting ROCM by 7.5-fold (Odds ratio 7.55, P $\frac{1}{4}$ 0.001).²⁵ In a multicenter observation study of 465 patients of mucormycosis from India, Patel et al. found that Diabetes mellitus was the dominant predisposing factor (present in 73.5% patients) in all forms of mucormycosis.²⁶

In the present study 78.7% patients were hospitalized for management of COVID-19 infection, 63.9% received inhalational oxygen therapy, 75.9% received injection steroid and 48.1% received injection remdesivir during treatment for COVID-19. In a study by Manda et al. steroid was administered in 94.8% of patients, oxygen therapy was given to 59.1% of patients and remdesivir was administered to 30.4% of patients.²⁰ In a study of 23 patients of post-COVID mucormycosis, Pathak et al. observed 82.6% patients had received steroid therapy during treatment for COVID.¹⁷ In a systematic review by John et al. 88% of patients with post-COVID mucormycosis received corticosteroids.²⁴ Singh et al. in a case series of 101 mucormycosis cases in Covid-19, found that 76.3% of the patients received a course of corticosteroids.²³ In another study of 171 patients, 80% of the patients received steroids during therapy and oxygen was administered to 71% of hospitalized patients.¹⁴

Corticosteroids are the only medication that had shown conclusively to be effective in the treatment of COVID-19 in clinical trials therapy. Systemic steroids could further hamper the underlying glycemic control as well as impede the body's immune system. High dose corticosteroid had been used in patients with COVID-19 disease and the use of such medications required assessment. One study showed that adherence to the use of low dose corticosteroid and good glycemic control were important in having no mucormycosis among 1027 ICU patients despite the use of corticosteroids in 89% and that 40% had diabetes mellitus. The presence of these pre-disposing factors in association with high fungal spore burden in certain localities and communities may set the perfect storm for the development of mucormycosis in patients with COVID-19.²⁷

Collectively, these findings suggest a familiar connection of mucormycosis, Diabetes mellitus and use of steroids, in people with COVID-19.

Singh et al. gave apparent triggers that may precipitate mucormycosis: Presence of Diabetes mellitus with or without Diabetic ketoacidosis (DKA) increases the risk of contracting mucormycosis. Uncontrolled hyperglycemia and precipitation of DKA is often observed due to corticosteroid intake. Low pH due to acidosis is a fertile media for mucor spores to germinate. Moreover, steroid use reduces the phagocytic activity of WBC. COVID-19 often causes reduction in CD4+ and CD8+ T-cell level. Hyperglycemia, increase in cytokines in patients with COVID-19 and concomitant acidosis increases free iron, which is an ideal resource for mucormycosis. High glucose, low pH, free iron, and ketones in presence of decreased phagocytic activity of WBC, enhances the growth of mucor. In addition, it enhances the expression of glucose regulator protein 78 (GRP-78) of endothelium cells and fungal ligand spore coating homolog (CoH) protein, enabling angio-invasion, hematogenous dissemination and tissue necrosis.²³

A probable reason for the surge in post-COVID-19 mucormycosis is the unhygienic delivery of oxygen or low-quality tubing system to these patients at the hospital intensive care units (ICUs), the oxygen cylinders with unclean masks, or using contaminated/tap water in humidifiers and prolonged usage of the same mask for more than two patients.²⁸ Thus non-sterile medical equipment delivering oxygen to the patient can be a source of fungal hyphae/spores leading to mucormycosis.

In the present study 65.74% patients showed presence of oral manifestations of mucormycosis. 30.6% patients had multiple draining sinuses over periodontium, 47.2% had swelling/ulcer/black eschar/bone exposure over palate or maxillary/mandibular bone and 54.6% showed pain/mobility/tenderness of teeth. In a study of 171 mucormycosis patients, Somkuwar et al. found 20% patients had hard palate findings, eschars, fistulas, and perforations, 38% had periodontal abscesses, and 5% reported tenderness to percussion.¹⁴ Ahmed et al. in a case series of 21 post-COVID-19 people with oral mucormycosis observed that oral signs of mucormycosis are often evident in the palate and may include varied degrees of mucosal staining, swelling, ulcerations, superficial necrotic regions in the palate, bone exposure, and necrosis with black eschar development. As a result, palatal ulcerations may be the first presenting symptom, prompting the patient to seek treatment from a dentist, who may be the first clinician to identify an infection, leading to the diagnosis of mucormycosis.¹³

Mucormycosis is a severe infection that requires the use of antifungal medications. In addition, it can require surgery to remove the infected tissue, leading to eventual loss of body parts like the upper jaw and even an eye. In some cases, mucormycosis treatment includes combination of surgical procedure and antifungal medicines.²⁹ Both surgical and antifungal therapeutic interventions have been carried out for the patients included in this study. FESS was performed in 97.2% patients, maxillectomy was performed in 50.9% patients, mandibulectomy was done in 2.78% patients. Orbital decompression was performed in 1.85% patients and orbital exenteration was performed in 7.41% patients. Prosthetic rehabilitation in the form of obturator with complete/partial denture was done for 14 patients who were treated with maxillectomy.

If the disease spreads from the maxillary sinus towards the oral cavity, it often causes angio-invasion of the palatal blood vessels leading to thrombosed necrotic black colored palate. The necrosis usually spreads towards the alveolus leading to destruction of the bone around the teeth causing tooth mobility and loss. Anterior and posterior spread from the sinus mucosa leads to destruction of the anterior and posterior wall of the maxilla, respectively. Involving these walls requires surgical debridement and removal, the extent of which is guided by the involvement of the bone by the fungus. Depending on the involvement and formation of bony sequestrum, the resection can be inferior/partial maxillectomy, sub-total maxillectomy with sparing of the orbital floor or total maxillectomy with resection of the orbital floor as well.¹⁶

Whenever the maxilla along with palate is resected, there is a resultant defect in the oral cavity leading to formation of an oro-nasal/oro-antral communication, which adversely affects the patient's quality of life in terms of mastication and phonation and therefore requires reconstruction in order to restore the normal functioning of the stomatognathic system. The reconstruction of the maxillary defects can be conducted through the fabrication of obturators, which can be tooth/mucosa supported or implant supported.¹⁶

Conclusion

Post-COVID mucormycosis is a challenging disease which emerged after the second wave of COVID-19 in India. In our study, we have analyzed 108 cases of post-COVID mucormycosis. Uncontrolled Diabetes mellitus, unmonitored usage of steroidal medications and use of non-sterile medical equipment could be responsible of the sudden increase in the cases of mucormycosis. The most common variant, rhino-orbital-cerebral mucormycosis initially involves paranasal sinuses and can spread to involve palate and maxilla, leading to the oral manifestations of the disease. Treatment involves antifungal therapy and surgical debridement of the necrotic tissue. Timely diagnosis, proper surgical and antifungal treatment, follow-up and rehabilitation can lead to better outcome for patients with mucormycosis.

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