

An Experience with Post Covid-19 Rhino-Orbital Cerebral Mucormycosis with Oral Manifestations: A Retrospective Study

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ABSTRACT

Background: The indiscriminate use of corticosteroids in moderate to severe COVID-19 cases has precipitated an unprecedented surge in mucormycosis, a life-threatening fungal infection. Although recent literature extensively discusses mucormycosis's clinical and treatment aspects, reports on its intra-oral manifestations remain sparse. This study aims to elucidate the presence and treatment of oral symptoms in Rhino-Orbital-Cerebral (ROC) mucormycosis cases.

Methods: A retrospective study was conducted utilizing 2021 records from the departmental OPD and IPD archives. Collected data encompassed demographic details, co-morbidities, predisposing factors, and both extra-oral and intra-oral symptomatology, as well as the treatments administered and the patient's status at least one-month post-hospital discharge. Numerical data underwent central tendency analysis, while chi-square testing was applied to ordinal data.

Results: Of the 21 ROC mucormycosis cases noted, most (20) presented with palatal lesions, one with a tongue lesion and two with maxillary alveolar involvement. Palatal afflictions included discoloration (4 cases), petechiae (4 cases), ulceration (7 cases), and necrosis (5 cases). Fourteen patients received medical therapy alone, and seven underwent additional surgical treatment. Survival and mortality rates showed no significant variation based on treatment type.

Conclusion: Early signs of ROC mucormycosis include intra-oral symptoms such as pain in the upper teeth, darkening of the palate, and tenderness in the alveolar region. Individuals, who have previously had COVID-19 and who have diabetes should promptly seek a medical or dental assessment if they experience these symptoms. The illness exhibits a significant mortality rate, with approximately one-third of the patients in this study leading to fatality.

Key-words: Amphotericin B; Mucormycosis; Post-COVID-19; Oral manifestation; Palate ulcer

INTRODUCTION

The era of COVID-19 brought uncertainty to the normal life of people, and doctors are no different. Lack of knowledge experience in dealing with a deadly pandemic

of such a magnitude, made doctors make choices which were not clinically proven or long-term side effects were not considered. One such concern was the emergence of post-COVID-19 mucormycosis, an epidemic in the pandemic. Platauff described mucormycosis or zygomycosis, a rare but deadly fungal disease in the late 19th century ^[1,2]. This fungus is usually found in damp or dusty places. It usually does not harm people with strong immune systems because macrophages effectively consume the spores. However, people dealing with specific health concerns or deficient immune systems are at an increased risk ^[3].

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The excessive prescription and improper administration of corticosteroids have been related to an increase in future infections, including fungal infections ^[2]. Individuals with pre-existing medical conditions such as asthma, diabetes, hypertension, or cardiovascular disorders are probable to experience severe complications from COVID-19. This also increases their susceptibility to secondary infections like mucormycosis ^[4].

There are five recognized subtypes of mucormycosis in medical literature, and Rhino-orbital-cerebral makes up one of them ^[7]. The literature reports a case fatality rate ranging from 30% to 70% ^[1,5,6]. Oral manifestation of lesions is infrequent and frequently overlooked by examiners, as medical practitioners or otolaryngologists typically diagnose these cases. This study aimed to determine the typical location in the mouth and oral symptoms associated with post-COVID-19 mucormycosis and identify different therapeutic approaches for this condition.

MATERIALS AND METHODS

A retrospective review was performed at the Department of Oral and Maxillofacial Surgery, Dental Institute, RIMS Ranchi, analyzing records from 1st January 2021 to 31st December 2021.

RESULTS

Table 1 summarises 21 cases of Rhino-Orbital-Cerebral (ROC) mucormycosis with oral manifestations, detailing patient demographics, co-morbid conditions, predisposing factors, specific intra-oral sites affected, treatment modalities, and outcomes. Most patients were male, with diabetes mellitus present in all cases.

Data Collection- Information was retrieved from OPD and IPD registers and recorded on a specially designed proforma, noting demographic data, co-morbidities, predisposing factors, and extra-oral and intra-oral clinical findings. The data also included the treatment modalities and patients' conditions at least one-month post-hospital discharge.

Inclusion Criteria- This study included patients post-COVID-19 infection with histological and radiological confirmation of mucormycosis.

Exclusion Criteria- Patients diagnosed with rhino-orbital-cerebral mucormycosis without clinical intra-oral presentation were excluded.

Classification of Lesions- Oral lesions were categorized into four stages based on their appearance in the palate: Stage 1- Discoloration, Stage 2- Petechiae, Stage 3- Ulceration, and Stage 4- Necrosis.

Ethical Considerations- The study followed ethical standards, with data confidentiality maintained. The institutional review board granted ethical approval for the study.

Hypertension was a common co-morbidity. Most treatments involved medical management with anti-fungal medication, while a subset required surgical intervention. The palate was the most affected intra-oral site. Outcomes varied, with a significant number of patients surviving, but a notable mortality rate was present.

Table 1: Summary of ROC mucormycosis with oral manifestation

Age	Sex	Co-morbidity	Predisposing factor	Intra-oral site	Treatment	Outcome of treatment
45	M	DM	Dmsone	Palate	Medical	D
55	M	DM, HTN	Dmsone	Palate	Medical	A
74	M	DM	Dmsone	Tongue	Medical	A
62	M	DM, HTN	None	Palate	Medical	A
45	F	DM, HTN	Dmsone	Palate	Medical+	D

					Surgical	
56	M	DM, HTN	Pslone	Palate	Medical	A
64	M	DM	Dmsone	Alveolus	Medical	D
42	F	DM	None	Palate	Medical	D
45	M	DM	Dmsone	Palate	Medical+ Surgical	A
41	M	DM	Dmsone	Palate	Medical+ Surgical	A
64	M	DM, HTN	None	Palate	Medical	A
58	F	DM	None	Palate	Medical	D
51	M	DM, HTN	Dmsone	Palate	Medical+ Surgical	A
59	M	DM	Dmsone	Palate	Medical+ Surgical	A
55	F	DM, HTN	Pslone	Palate	Medical	A
64	M	DM	Dmsone	Palate	Medical+ Surgical	D
44	M	DM	None	Palate	Medical	A
50	M	DM	Pslone	Palate	Medical	A
56	M	DM, HTN	Dmsone	Palate	Medical+ Surgical	A
65	F	DM	Dmsone	Palate	Medical	D
46	F	DM	Dmsone	Alveolus, Palate	Medical	A

****Dmsone – Dexamethasone, Pslone – Posaconazole, DM – Diabetes mellitus, HTN- hypertension, A- Alive, D - Deceased.**

Table 2 shows the stages of palate involvement in patients suffering from ROC mucormycosis. It categorizes the intra-oral lesions into four distinct stages: Discoloration, Petechiae, Ulceration, and Necrosis, reporting the number of patients and corresponding percentages for each stage. The table indicates that the most common manifestations were Ulceration and Necrosis, suggesting a progression toward more severe forms of the disease in a significant portion of the cases.

Table 2: Stages of palate involvement

Stage of Palate involvement	No. of patient	Percentage (%)
Stage 1 (Discoloration)	4	20
Stage 2 (Petechiae)	4	20
Stage 3 (Ulceration)	7	35
Stage 4 (Necrosis)	5	25

We came across 21 patients that met our specific criteria for inclusion and exclusion. There were 15 male patients and 6 female patients. The median age of these individuals was 54.33 years. The patients' summarized presentation is displayed in Table 1.

Predisposing factors and co-morbidities- All 21 patients had diabetes mellitus. Along with them 8 patients had hypertension as co-morbidity. 17 patients were given corticosteroids during the treatment of COVID-19, dexamethasone was given in 14 patients and prednisolone in the rest 3.

Clinical features- All the patients had extra-oral signs such as swelling, proptosis, chemosis, subconjunctival haemorrhage, skin necrosis or eye blindness. Intra-orally, most of the patients (20) had lesion in the palate, discoloration of the palate alone was seen in 4, Petechiae was seen in 4, palatal ulceration was present in 7 and 5 patients had severe necrosis of the palate with visible oro-nasal communication (Table 2). Apart from these, one patient had a lesion in the maxillary alveolus and one had haemorrhage in the lateral and posterior tongue (Fig. 1).

Treatment- Fourteen patients were given medical treatment alone. The remaining 7 patients received surgical intervention along with medical treatment. Medical treatment consisted of anti-fungal medication of liposomal Amp B and oral mucorales, or combinations of the above-mentioned anti-fungal drugs. Systemic antibiotics were also prescribed to a few patients, non-steroidal anti-inflammatory drugs (NSAID) or opioids for pain relief, and other drugs were given for specific patient needs. A povidone-iodine mouth gargle was prescribed for oral hygiene. Surgical treatment consisted of surgical debridement of the lesion in 4 cases and maxillectomy in 3 cases.

Treatment outcome- Out of all the 21 patients treated, 14 survived and 7 died. Among the 14 patients who got exclusive medical treatment, 9 survived and 5 got deceased, whereas out of 7 patients requiring surgery as well, 5 survived and 2 died during follow-up. Chi-square value was found to be 0.007 with a p-value of 0.93, which was statistically insignificant.

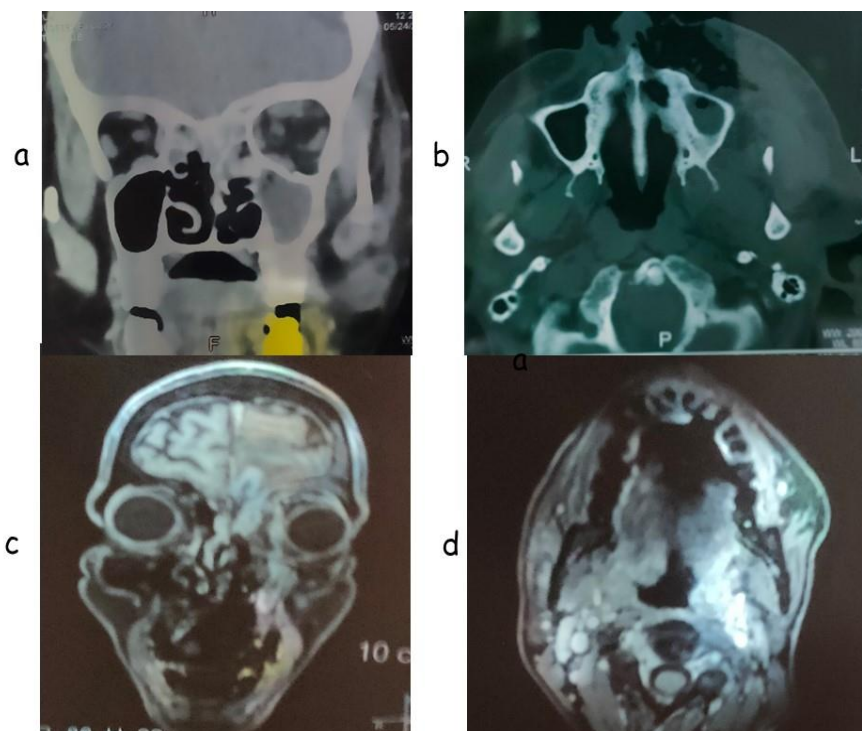


Fig. 1: CT and MRI presentation of ROC mucormycosis- (a) coronal section CT, (b) axial section CT, (c) coronal section MRI, (d) axial section MRI

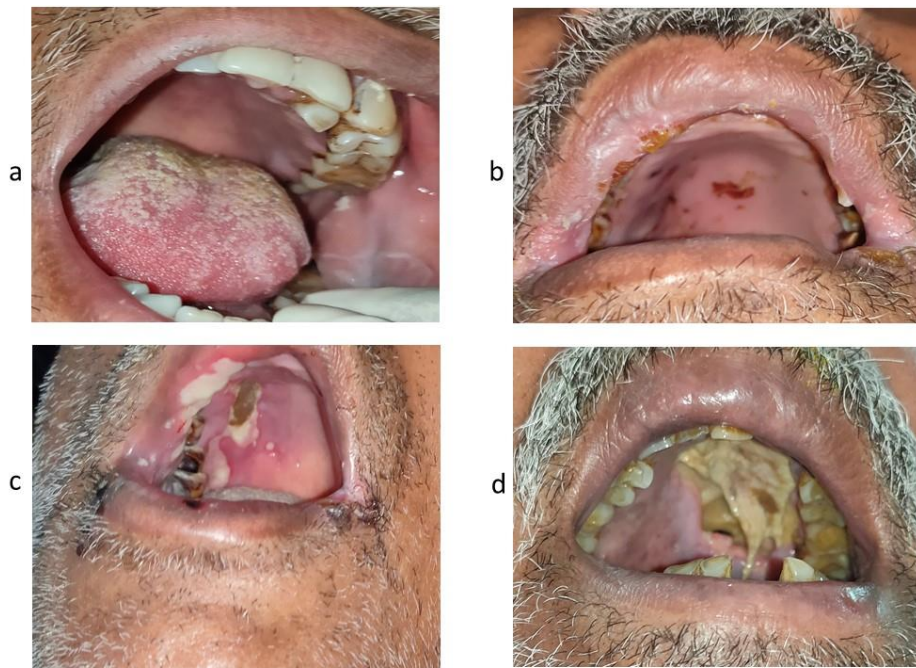


Fig. 2: Clinal stages of palate involvement seen in 4 different male patients- (a) Discoloration, (b) Petechiae, (c) Ulceration, (d) Necrosis

DISCUSSION

Outbreak of post-pandemic mucormycosis was seen in many countries, but it hit hard in India, where many states had declared it as an epidemic. According to a report, 45374 infected cases and more than 4300 deaths have been recorded so far within the country till 21st July 2021 [8]. A deadly trio of COVID-19, diabetic and corticosteroids is already known as causative factors for post-COVID-19 mucormycosis. Data obtained from our study further confirms this association. Some literature suggested that the absence of diabetes and corticosteroids does not guarantee a shield from post-COVID-19 mucormycosis. Isolated cases have shown that ROC mucormycosis can present in the host without any underlying disease. COVID-19 reacts to everyone's physiology differently, increasing blood glucose and decreasing the host defence mechanism [9].

Innate immunity is altered in the diabetic population, particularly in acidosis, as reflected by well-characterized polymorphonuclear (PMN) dysfunction. The immune response from PMN starts as soon as spores invade tissues. If mucorales spores encounter an immune system in good condition, phagocytic cells will devour the spores using the alternative complement pathway. Studies have proved that hyperglycemia and acidosis can impair the ability of phagocytes' to mobility and virulence towards spores through oxidative and non-

oxidative mechanisms [10]. Iron metabolism, known to be modified in diabetes, plays a central role in Mucorales virulence. Platelets also play a role in damaging Mucorales hyphae in a time-dependent manner [11]. However, platelet function is altered in diabetic patients through structural and functional modifications of the platelet-membrane properties and alterations of nitric oxide metabolism. All the above explains the increased susceptibility of mucormycosis in patients with impaired glycaemic control.

Most cases of mucormycosis reported in India or elsewhere are diagnosed by the ophthalmologist, otolaryngologist or medical practitioner. They take clear, visible notes of facial presentations like oedema, ptosis, chemosis, septal deviation, or neurological involvement, but there is a possibility that oral presentation is missed. In many but not all cases which report extensive facial involvement, the absence of oral manifestations suggests the same. In this study, we reported noticeable oral signs. Few patients have shown worsening of their presentation even after administration of a standard anti-fungal regimen, starting from blackening and finally becoming ulceration in the palate. In a few studies, oral manifestations can be the only sign during the initial stage of the disease. Hence, we recommend that any dental pain or palatal discoloration in susceptible patients be thoroughly reviewed with CT or MRI before

ruling out the deadly black fungus ^[12]. Palatal involvement of the lesion was the most common oral finding of ROC mucormycosis. All four stages of palatal involvement have a distinct presentation. The lesion can also be seen in the tongue, maxillary alveolus, or lips ^[13]. Sometimes, maxillary sinuses are the first to get infected, causing erosion of their boundaries. In the course of the progression of the disease, when superior alveolar nerves are encountered, they can give symptoms mimicking dental infections. We encountered several patients with dental pain in maxillary teeth, but no oral lesions were seen during the examination. A wide range of periods were recorded between onset of COVID-19 and mucormycosis, but as data for all the patients were unavailable, it was excluded from the study.

Treatment of ROC mucormycosis includes anti-fungal therapy, either oral or parenteral, from superficial surgical debridement to aggressive resection of bones involved and care to predisposing factors. The suggested first-line anti-fungal treatment is a lipid-based Liposomal AmpB formulation (1 to 5mg/kg/day). In contrast, broad-spectrum azoles, such as Posaconazole (300mg BD loading dose followed by 300 mg OD), are regarded as second-line or adjunctive therapy ^[14]. Caspofungin 70mg intravenous (IV) load followed by 50 mg/day, Mucafungin 100mg/day, Deferasirox 20mg/kg po once daily is also recommended in adjuvant with lipid proline in few protocols ^[15]. Posaconazole has shown success as salvage therapy for mucormycosis patients after Amp B failure or in patients with renal failure. In the present study, Liposomal Amp B was used in all patients.

Steroids have value; they have been proven lifesaving in many cases of COVID-19. However, the absence of a universally accepted protocol and non-judicial use of corticosteroids has created an alarming situation in a few places on the world's map. Dexamethasone and methylprednisolone are commonly used in treatment procedures for COVID-19, particularly for patients with moderate to severe instances ^[16]. Glucocorticoids have an immunosuppressive effect, which increases patients' vulnerability to secondary infections. It may be necessary to reconsider the usual procedure for giving steroids to treat Covid-19 infection, and it is essential to emphasise the need for strict control of blood sugar levels before and after Covid-19 infection ^[17,18].

The cost of the treatment for mucormycosis is quite high, both physically and financially, to the patient. Even after

survival, amputation of an eye or a part of the mid-face can leave a burden of a lifetime. Being in a government-funded hospital, patients didn't have to buy any medicine from outside, but a few times, when the stock got over, it was too expensive for poor patients to buy even one dose of the drug. In India, where the average income is 1947\$, the cost of Liposomal amphotericin B for 20 vials could be 1650\$, which would last for 5 days of treatment for a 60 kg adult. Treatment protocols suggest a course of >2 weeks of the anti-fungal medications. In surgical management, maxillectomy was done in 3 cases, and 4 others underwent surgical debridement under general anaesthesia. Even with treatment with expensive medicine and aggressive surgical treatment, the disease has a high mortality rate. Around one in every three patients died during the treatment (7 out of 21 outcomes) ^[19,20].

Another important outcome of this study was the patient's prognosis irrespective of the type of treatment, medical or medical, along with surgical intervention. Although a slightly higher percentage of patients survived, 5 out of 7 (72.5%) received surgical and medical treatment compared to 9 out of 14 (62.5%) who received only a medical line of treatment. Statistical analysis showed non-significant association between death and the treatment provided.

CONCLUSIONS

This research illuminates the profound consequences of mucormycosis, specifically its oral manifestations, in the aftermath of COVID-19. It emphasises a direct correlation between corticosteroid use and pre-existing diabetes. The observation that palatal lesions frequently serve as an initial sign of the infection emphasises the criticality of prompt dental examinations for susceptible individuals.

Notwithstanding the existence of various treatment modalities, the disease's severity is shown by the high mortality rate, which further emphasises the critical nature of early detection and intervention. The results emphasise the importance of close monitoring of post-COVID patients, particularly diabetics, and cautious steroid use to prevent the establishment of this dangerous fungal infection.

CONTRIBUTION OF AUTHORS

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Final approval- Dr. Arun K Goyal

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