**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 67175

**Manuscript Type:** CASE REPORT

**Mucormycosis–resurgence of a deadly opportunist during COVID-19 pandemic: Four case reports**

Upadhyay S *et al*. Post-COVID oral mucormycosis

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**Author contributions:** Upadhyay S, Bharara T and Khandait M reviewed the literature and contributed to manuscript drafting; Upadhyay S, and Bharara T performed the microbiological analyses and interpretation; Chowdhry A was the oral and maxillofacial surgeon who took the history and performed detailed analysis of the cases; Sharma B analyzed and interpreted the imaging findings; Khandait M and Bharara T performed the revision of the manuscript for important intellectual content; All authors have read and approve the final manuscript.

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**Received:** April 17, 2021

**Revised:** August 6, 2021

**Accepted:** **November 5, 2021**

**Published online:**

**Abstract**

BACKGROUND

Coronavirus disease 2019 (COVID-19) patients who suffer severe infection or comorbidities have an increased riskof developing fungal infections. There is a possibility that such infections are missed or misdiagnosed, in which case patients may suffer higher morbidity and mortality. COVID-19 infection, aggressive management strategies and comorbidities like diabetes render patients prone to opportunistic fungal infections. Mucormycosis is one of the opportunistic fungal infectionsthatmay affect treated COVID patients.

CASE SUMMARY

We present a case series of four adult males who were diagnosed with mucormycosis post-COVID-19 recovery. All the patients had diabetes and ahistory of systemic corticosteroids for treatment of COVID-19. The mean duration between diagnosis of COVID-19 and development of symptoms of mucor was 15.5 ± 14.5 (7–30) d. All patients underwent debridement and were started on antifungal therapy. One patient was referred to a higher center for further management, but the others responded well to treatment and showed signs of improvement at the last follow-up.

CONCLUSION

Early diagnosis and management of mucormycosis with appropriate and aggressive antifungals and surgical debridement can improve survival.

**Key Words:** Zygomycetes; Fungal infection; COVID-19 co-infection; Diabetes mellitus; Case series; Case report

Upadhyay S, Bharara T, Khandait M, Chawdhry A, Sharma BB. Mucormycosis - resurgence of a deadly opportunist during COVID-19 pandemic: Four case reports. *World J Clin Cases* 2021; In press

**Core Tip:** Mucormycosis usually indicates a serious underlying medical condition such as diabetes. Furthermore, the immune dysregulation post coronavirus disease 2019, and widespread use of immunosuppressants and broad-spectrum antibiotics may lead to enhanced susceptibility to a number of secondary opportunistic infections such asmucormycosis. Clinical suspicion along with prompt microbiological diagnosis are indispensable to a positive case outcome.

**INTRODUCTION**

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is known to infect alveolar epithelial cells (pneumonia and acute respiratory distress syndrome) as well as monocytes/macrophages leading to a cytokine storm (multiorgan failure and death)[1]. The cytokine storm seen in severe cases has led to increased use of steroids and other immunosuppressive therapy in moderate-to-severe cases. Coronavirus disease 2019 (COVID-19) infection, aggressive management strategies and comorbidities such asdiabetes mellitus (DM) render patients prone to opportunistic fungal infections[2,3].

Mucormycosis is a deadly and rapidly progressive fungal infection of humans. The usual presentation is rhinocerebral mucormycosis[4]. Oral mucormycosis is an unusual manifestation of the disease mainly affecting immunocompromised patients such as those with DM, corticosteroid treatment, leukemia, lymphoma, human immunodeficiency virus (HIV) infection*etc.*[3,5,6]. Although there are few publications on fungal co-infections associated with COVID-19, it is pertinent to point out that there is a high chance of missed or misdiagnosis in these cases.

To analyze mucor infections in COVID-19 patients, we searched PubMed, Scopus and Web of Science, using the keywords ‘‘mucor’’, ‘‘mucormycosis’’, ‘‘opportunistic fungal infection’’, ‘‘oral fungal infections’’, ‘‘post COVID infection’’, ‘‘COVID-19’’ or ‘‘SARS-CoV-2’’ (up to April 16, 2021). Through this report,we provide an insight into clinical features, laboratory diagnosis and significance of timely management of post-COVID mucormycosis infection through a series of four cases who presented to the outpatient department of our hospital.

**CASE PRESENTATION**

***Chief complaints***

All the cases presented to the department of oral and maxillofacial surgery with chief complaints of pain, swelling and pus discharge from their oral cavity.

***History of present illness***

**Case 1:**a 39-year-old manpresented to the outpatient department (OPD) complaining of pain and mobility in the teeth of the upper jaw region for thepast 2 mo. The patient gave a history of extraction of a tooth in the upper jaw 2 mo previously, after which he developed a nonhealing painful lesion. The pain gradually spread to the entire left maxilla (Figure 1A).

**Case 2:**a 57-year-old manpresented to the OPD with gingival swelling and multiple draining sinuses on right and left anterior maxilla and right side of the palate for the past 1 wk (Figure 1B). The patient presented to the OPD with the same complaints 1wk previously and was prescribed antibiotics, however, he did not obtainany relief.

**Case 3:**A 45-year-old man presented to the OPD with chief complaints of pain, bleeding and ulcers in the gums.

**Case 4:**a 55-year-old man presented to the OPD with chief complaints of pus discharge and bleeding from the gums (Figure 1C).

***History of past illness***

All four patients had a history of uncontrolled DM. All the cases gave a past history of suffering from COVID-19 that dated back 2–3 mo. Case 1 suffered from COVID-19 3mo back.Case 2 was hospitalized for 17 d for treatment of COVID-19. He developed the mucosal lesions 9 d after recovery from COVID-19. Case 3 tested positive for SARS-CoV-2 3 mo back, andhe recovered from the viral infection after 15 d of treatment. He noticed the presenting lesions 1 wk after recovery from COVID-19 infection. Case 4 was apparently well 2 mo back when he tested positive for SARS-CoV-2 through RT-PCR. He recovered from the viral infection after 10 d of treatment. The patient developed the present lesions 16 d afterrecovery from COVID-19.

***Physical examination***

All the patients were afebrile at presentation. In Case 1, bothmaxilla showed the presence of pus-discharging sinuses. The patient’s mouth opening was found to be adequate. Case 2 showed gingival swelling and multiple draining sinuses on both anterior maxilla and also the right side of the palate. Case 3 demonstratedgingival swelling and multiple draining sinuses on both anterior maxilla and theright side of the palate. However, his mouth opening was inadequate. Case 4 had multiple sinus formation on gingiva and discoloration of the hard palate was observed (Figure 1C). On palpation,a maxillary fragment was mobile.

***Laboratory examinations***

Blood chemistry, arterial blood gas analysis, urinalysis, electrocardiographyand chest X-ray were normal in all four cases.

**Further diagnostic work-up:** All fourcases tested negative for HIV antibody, hepatitis B surface antigen, and hepatitis virus antibody. Complete blood count, liver function test and kidney function test were within normal ranges.

**Microbiological identification of the causative agent:** The tissues/pus samples from the lesions were analyzed by direct microscopy and culture (Figure 2). The potassium hydroxide (KOH) mount of direct specimens showed broad aseptate hyaline hyphae. The tissue specimens from maxillary sinuses of all the cases showed granulomatous reaction with thick, broad fungal hyphae suggestive of *Mucor* spp.The specimens were cultured on Sabouraud dextrose agar (SDA) and culture tubes were incubated at 37ºC and 25ºC. After 5–10 d of incubation, there was cottony white growth on SDA. Lactophenol cotton blue (LPCB) staining showed broad aseptate hyphae in all four cases.

***Imaging examinations***

**Case 1:** Noncontrast computed tomography (NCCT) of paranasal sinuses (PNSs) showed bony defects involving the left side of the alveolar process of the maxilla, and the anterior medial and lateral walls of the left maxillary sinus showed thinning and attenuation/erosion. Findings revealed residual/recurrent fungal sinusitis.

**Case 2**:NCCT of the PNSs showed bony septa in the right frontal sinus withmucosal thickening and air locules (Figure 3). The right osteomeatal complex was obliterated with adjacent bone erosion and erosion of the medial wall of the right maxillary sinus.

**Case 3:**Imaging could not be performed as he was referred to a higher center before the investigation could be performed.

**Case 4:** NCCT of the PNSs showed bony erosion involving both sides of the alveolar process of the maxilla.

**MULTIDISCIPLINARY EXPERT CONSULTATION**

***Ankit Chowdhry, MDS, Post Graduate student, Department of Oral and Maxillofacial Surgery, SGT University***

**Case 1:** Surgical debridement of the left maxilla, bullectomy and left ethmoidectomy was performed under general anesthesia.

**Case 2:**The patient was started on amoxicillin–clavulanic acid (500/125 mg 12 h) and liposomal amphotericin B (5 mg/kg in 10% dextrose).

**Case 3:**The patient was started on liposomal amphotericin-B (5 mg/kg in 10% dextrose). Since the patient needed extensive surgery, he was referred to a higher center for further management.

**Case 4:** The patient was started on liposomal amphotericin B (5 mg/kg in 10% dextrose).

***Tanisha Bharara, MD, A******ssistant Professor, Department of Microbiology, SGT University and Shalini Upadhyay, MD, Assistant Professor, Department of Microbiology, SGT University***

The microbiological analysis of pus and tissue specimens showed fungal hyphae in KOH mount. The growth on SDA and LPCB appearance wassuggestive of *Mucor* spp.

***Manisha Khandait, MD, Professor and Head, Department of Microbiology, SGT University***

Mucormycosis should be treated with liposomal amphotericin B.

***Bharat Bhushan Sharma, MD, Professor and Head, Department of Radiodiagnosis, SGT University***

NCCT of PNSswassuggestive of structural changes due to mucormycosis.

**FINAL DIAGNOSIS**

The final diagnosis of the four cases was post-COVID oral mucormycosis.

**TREATMENT**

All the patients were started on intravenous infusion of liposomal amphotericin B at aninitial dose of 5 mg/kg diluted in 10% dextrose. Cases 1 and 3 needed additional surgical intervention. The cases were followed up for clinical and radiological resolution of active disease.

**OUTCOME AND FOLLOW-UP**

Cases 1, 2and 4responded well to treatment. Case 3could not be followed up as he was referred to a higher center.

**DISCUSSION**

We report a series of four cases of oral mucormycosis among male patients with DM. Mucormycosis sometimes appears as a diabetes-defining illness and remains one of the most devastating complications in uncontrolled DM. India contributes to 40% of the global burden of this deadly opportunistic infection, with an estimated prevalence of > 100 cases per million population[4]. All patients in this study hadDMand similar oral lesions, andwere diagnosed with the help of laboratory tests and NCCT. Two of the patients needed surgical debridement and all four were treated with liposomal amphotericin B. The patients showed improvement in their lesions. One of the patients who had extensive lesions was referred to a higher center for further care.

Huang *et al*[7]reported a case of oral mucormycosis and extensive maxillary osteonecrosis secondary to dental extraction in a 40-year-old immunocompromised patient. The author emphasized early recognition and aggressive treatment of such patients in order to prevent morbidity and mortality[8]. Fogarty *et al*[9]and Kumar *et al*[10] also reported development of oral mucormycosis among elderly immunocompromised men. Various cases of oral mucormycosis reported so far are summarized in Table 1[11-17].

Another peculiar finding observed in our study was that all the patients gave a past history of COVID-19. SARS-CoV-2 is capable of infecting not only intraepithelial cells within the lungs, but also causes an abortive infection of the macrophages and dendritic cells. This leads to a storm of proinflammatory cytokines thatrenders the patient prone to opportunistic infections such asmucormycosis[1]. Invasive mucormycosis has not only been reported in severe cases but even in mild-to-moderate COVID. Although a few cases of oral mucormycosis have been reported in the literature, this is one of the first case series reported among COVID-19 patients.

Mucormycosis suggests the presence of a pre-existing immunosuppressive condition such as diabetes, leukemia, lymphoma, renal failure, immunosuppressive therapy, malnutrition, viral infection and severe burns. Hyperglycemia due to uncontrolled diabetes is the strongest risk factor for development of mucormycosis. It leads to polymorphonuclear dysfunction, defective chemotaxis and dysregulated intracellular killing. In ketoacidosis, free iron becomes readily available in the serum, which is efficiently taken up by *Mucor*for its growth and virulence. The association between DM and COVID is a known fact[18]. Corticosteroid use in severe COVID-19 patients with diabetes further impairs the functioning of neutrophils, thus making these patients highly susceptible to development of mucormycosis[3,5,17,18].

Inhalation of fungalspores or direct wound contamination are the two most common causes oforal mucormycosis[19,20]. The most common form of this disease ismaxillofacial. Early symptoms of this disease include facial cellulitis, periorbital edema and nasal inflammation, followed by widespread tissue necrosis[21]. Failure of prompt medical and surgical intervention may lead to cerebral spread, cavernous sinus thrombosis, septicemia and multiple organ failure,resulting in high morbidity and mortality[22].

Suspicion of mucormycosis is based on laboratory and imaging findings, risk factors and disease progression while on any antibacterial or antifungal therapy that does not cover *Mucor*infection. The pathognomonic feature of mucormycosis is tissue necrosis manifesting as a necrotic lesion, eschar or black discharge in the nasal or oral cavity[23].

Rapid diagnostic methods include biopsy, KOH mount and Calcofluor stain. Since it is difficult to routinely culture *Mucor*, biopsy is preferred for confirmation of diagnosis[2,21,23] (Figure 4). Management includes antifungal therapy, surgical debridement, diagnosisand treatment ofthe underlying predisposing factors, and adjuvant therapy. Amphotericin B is the standard treatment for invasive mucormycosis[24]. Posaconazole or isavuconazole may be preferred in COVID-19 patients with acute on chronic renal failure. Isavuconazole shortens the QT interval, which may be affected by hydroxychloroquine and azithromycin therapy commonly used in COVID-19 patients[25]. Adjuvant therapy like caspofungin, deferasirox, statins, aspirin, and hyperbaric oxygen may be added as adjunctive treatment[26].

Clinical suspicion, meticulous diagnosis, coordination between different medical departments and timely intervention werethe strengths of our study. Limitation of the study werethat antifungal susceptibility testing and further molecular characterization of the isolated fungal pathogen could not be done due to limitation of resources.

**CONCLUSION**

Clinicians should be familiar with presentations of rare opportunistic fungal infections and keep a high index of suspicion in post-COVID patients with DM. A multidisciplinary approach facilitating early diagnosis, aggressive surgical intervention, medical treatment with amphotericin B and controlling DM are the mainstay for improving the outcome of patients with mucormycosis in post-COVID patients. The incidence of oral mucormycosis may increase, either as co-infection or as a sequela of COVID-19. Therefore, urgent reporting of any new information is of importance to keep the scientific community abreast with what all can go wrong post-COVID infection, which till now is unexplored territory.

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**Footnotes**

**Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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**Manuscript source:** Unsolicited manuscript

**Peer-review started:** April 17, 2021

**First decision:** July 15, 2021

**Article in press:**

**Specialty type:** Infectious diseases

**Country/Territory of origin:** India

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

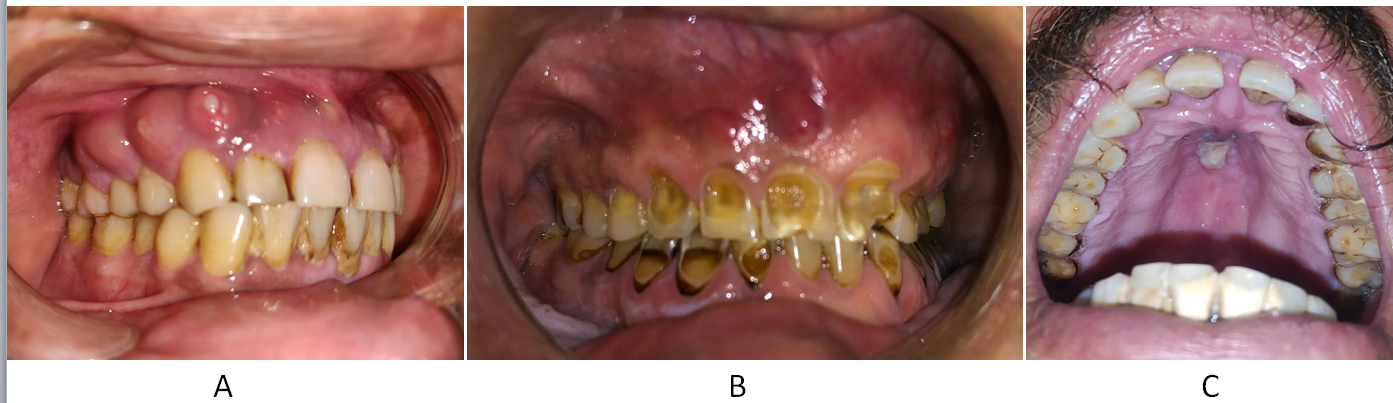
Grade C (Good): C

Grade D (Fair): 0

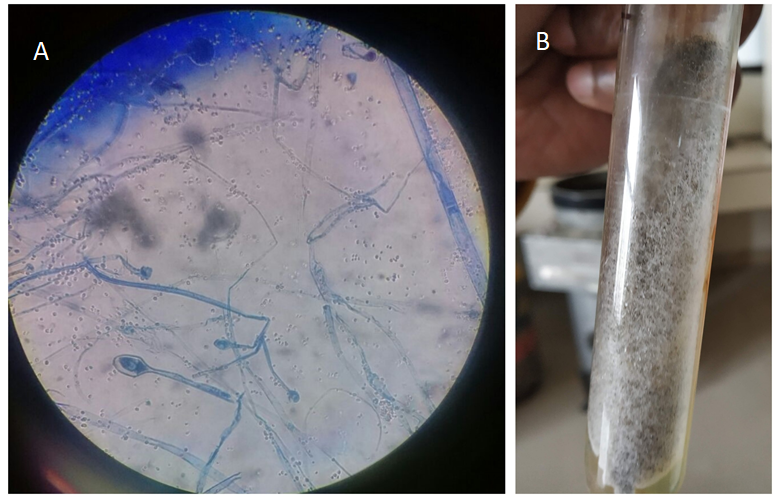
Grade E (Poor): 0

**P-Reviewer:** Bhatt KP **S-Editor:** Ma YJ **L-Editor:** Kerr C **P-Editor:** Ma YJ

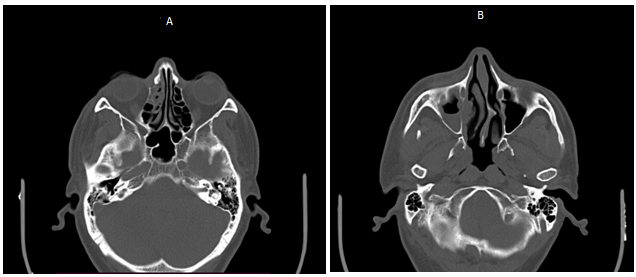
**Figure Legends**



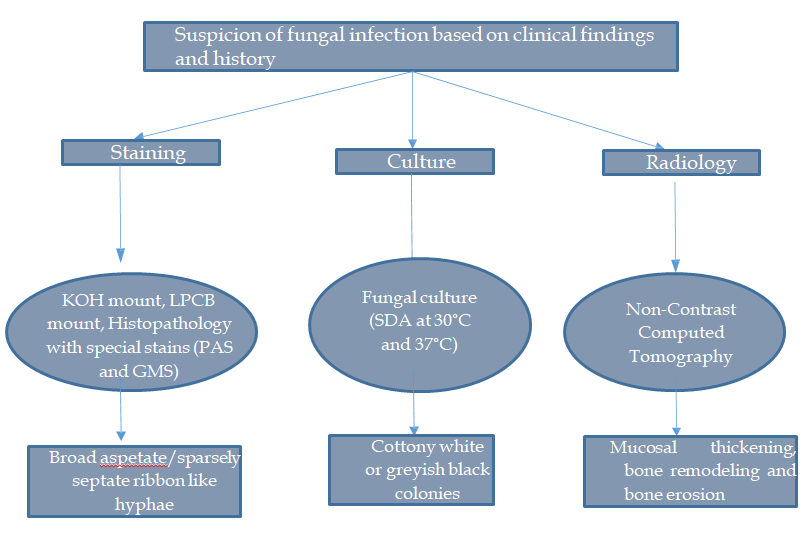
**Figure 1 Clinical picture of oral mucormycosis.** A: Multiple lesion on gingiva (Case 1); B: Erythema and multiple pus discharging sinuses on gingiva (Case 2); C: Discoloration of hard palate (Case 4).



**Figure 2 Staining and culture characteristics of mucormycosis.** A: Broad ribbon like aseptate hyphae seen on lactophenol cotton blue staining; B: Whitish grey cottony growth on Sabouraud’s dextrose agar.



**Figure 3 Noncontrast computed tomography of paranasal sinuses.** A: Axial section showing mucosal thickening and bone remodeling involving ethmoidal sinus on right side; B: Axial section showing mucosal thickening on right maxillary sinus with remodeling of medial wall.



**Figure 4 Flow chart for diagnosis of mucormycosis[21,23].**KOH: Potassium hydroxide; LPCB: Lactophenol cotton blue; PAS: Periodic acid–Schiff; GMS: Grocott-Gomori's methenamine silver; SDA: Sabouraud dextrose agar.

**Table 1 summary of cases of mucormycosis associated with coronavirus disease 2019**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Ref.** | **Country** | **Age (yr)/sex** | **Site** | **Comorbidities** | **Outcome** |
| Mehta *et al*[11] | India | 60/Male | Rhino-orbito-cerebralmucormycosis | Uncontrolled diabetes | Death |
| Werthman *et al*[12] | United States | 33/Female | Rhino-orbito-cerebralmucormycosis | Diabetes, asthma,  hypertension | Death |
| Hanley *et al*[13] | United Kingdom | 22/Male | Disseminated (involving the hilarlymph nodes, heart, brain, andkidney)/NA | Pancreatitis | Death |
| Placik *et al*[14] | Arizona | 49/ Male | Pulmonarymucormycosis | None | Death |
| Monte *et al*[15] | Brazil | 86/Male | Gastrointestinalmucormycosis | Hypertension | Death |
| Mekonnen *et al*[16] | United States | 60/Male | Rhino-orbitalmucormycosis | Diabetes, asthma,  hypertension,  hyperlipidaemia | Death |
| Pasero *et al*[17] | Italy | 66/Male | Sinopulmonary mucormycosis | Lymphopenia, Hypertension | Death |
| This case | India | 4 males, 49 ± 10 (39–57) | Oral mucormycosis | Diabetes mellitus | 3 alive, one lost to follow up |