

# Management of Post COVID-19 Rhino cerebral Mucormycosis: A case report

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## Case Report

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## **Abstract**

Mucormycosis is a life-threatening, opportunistic, deep fungal infection frequently evident in patients with moderate to severe forms of COVID-19. It is usually detected within 2-8 weeks after the onset of symptoms and is categorized into six types depending on its location. The rhinocerebral form is most prevalent and involves orofacial structures. The fulminant nature of Mucormycosis necessitates rapid diagnosis and aggressive multidisciplinary treatment planning. This report presents a case of post-COVID-19 rhinocerebral Mucormycosis, where the failure to identify the disease by the dentist led to treatment delay. The patient was successfully managed by a combined approach of surgical debridement and systemic antifungal drug administration. The function and esthetics were restored by prosthetic rehabilitation. Etiopathogenesis of post-COVID-19 Mucromycosis and the dentist's role in the diagnosis and treatment of mucormycosis following COVID-19 infection is discussed.

## **Introduction:**

Coronavirus disease (COVID-19) is a respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).<sup>1</sup> Based on the severity of the disease, COVID-19 patients are classified into mild, moderate, severe, and critical cases.<sup>2</sup> Lymphopenia is the central laboratory finding in most severely ill COVID-19 patients, and steroids are frequently prescribed to suppress the cytokine storm in these patients.<sup>3,4</sup> Thus, the compromised immune response makes them vulnerable to opportunistic infections. Mucormycosis is one such life-threatening, opportunistic, deep fungal infection frequently evident in patients with moderate to severe forms of COVID-19.<sup>5</sup> It is usually detected within 2-8 weeks after the onset of COVID-19 symptoms and is categorized into six types depending on its location. The sinuses are the most often affected location (39 per cent), resulting in the rhino-cerebral form of mucormycosis.<sup>6</sup> The patient presents with unilateral proptosis, swelling of the periorbital and perinasal tissues, dilation and fixation of the pupil, paranasal sinusitis, and cranial nerve involvement.<sup>7</sup> The oral manifestations of rhinocerebral mucormycosis are described as blackish discolouration of palatal mucosa, pressure ulcers in the palate or floor of the mouth, presence of necrotizing plaque, gingival abscess, and development of sudden mobility of teeth.<sup>8,9</sup> Aggressive surgical debridement and resection of involved areas create defects that compromise function and aesthetics. This article describes the diagnosis and management with emphasis on oral rehabilitation of a case of post-COVID-19 rhino-cerebral mucormycosis.

## **Case Report:**

A 30-year-old male reported to our emergency department with a complaint of pain and swelling in the left cheek and pus discharge from the oral cavity for two weeks. The patient had a positive history of COIVD-19 diagnosed by RT-PCR test. The patient was hospitalized for ten days, where he received steroids (tablet Methylprednisolone 16mg BD for five days) and supportive oxygen therapy and was discharged after a negative RT-PCT report for SARS-CoV-2. A week after the discharge, the patient experienced dull pain in the left maxillary posterior teeth, which became mobile after two days. He visited

a general dental practitioner who initiated root canal treatment in the left maxillary first and second premolar and molar teeth. After multiple appointments for almost one month, the patient was not relieved of his pain and noticed pus discharge from the sulcus area. He visited another dentist, who extracted the left maxillary second premolar tooth. One week after the extraction, the patient developed a swelling on the left side of the face and reported to the emergency department. Contrast-Enhanced Computed Tomography (CECT) scan of the face revealed diffuse erosion of the walls of the left maxillary sinus, floor of the orbit, palatine part of left maxilla, and multiple geographic lytic lesions (Figure 1). These findings were suggestive of left maxillary osteomyelitis with associated soft tissue/ sinonasal Mucormycosis. The pus KOH was negative; therefore, a provisional diagnosis of bacterial osteomyelitis of the left maxilla was made, and systemic antibiotic therapy was initiated, planned for surgery and underwent debridement via sub labial approach. The procedure was explained to the patient and written informed consent was obtained. The necrotic anterior wall of the maxilla and the alveolar process was removed along with the left maxillary canine, premolar, and molars (Figure 2). The histopathologic examination of excised tissue showed the presence of hyaline aseptate hyphae, which were suggestive of mucormycosis. Systemic antifungal medication (inj. Liposomal amphotericin B) was started immediately. During the hospital stay, the patient complained of mobility of remaining maxillary teeth on the left side and for which a dental referral was made. On intraoral clinical examination, left maxillary incisors were grade II mobile and did not respond to the electric pulp test. An intraoral periapical radiograph revealed a diffuse radiolucent lesion with relation to left maxillary central and lateral incisors (Figure 3A&B). A diagnosis of pulp necrosis was made, and radiographic lesions were considered as representations of mucormycosis. The access opening was made and extirpated pulp tissue was sent for histopathologic examination. Histology revealed dense fibrotic pulp tissue with interspersed numerous basophilic diffuse calcifications showing peripheral stromal retraction, mild lymphoplasmacytic infiltrate, and congested blood vessels suggestive of necrosis of pulp with pulpal calcifications (Figure 3C). Periodic acid-Schiff (PAS) and Grocott's methenamine silver stain (GMS) showed no fungal organisms in the pulp tissue. Calcium hydroxide was used as an interappointment intercanal medicament, and the root canal treatment was completed in two visits. A CECT scan was repeated after completing the cumulative target of 3g of Liposomal Amphotericin, which showed some residual disease with osteomyelitic bone involving zygoma and remnant of maxillary bone on the left side. The lesion was debrided entirely during the second surgery, along with excision of a part of the left zygomatic bone and the left maxillary lateral incisor extraction. After the initial healing of the surgical site and stabilization of the disease, the patient was discharged with advice to use oral antifungals (Posaconazole tablet 300mg /day) for one month.

The iatrogenic oroantral fistula created after surgical debridement was classified as Armany class II defect and managed by obturator prosthesis (Figure 4A&B). After the initial healing of the surgical site, an alginate impression (Algiplast, DPI, Mumbai, India) of the maxilla was made, extending into the surgical defect and covering all the defect's margins, blocking all unfavourable margins undercuts with a wet gauge piece. The cast was obtained by pouring the impression with type III dental stone (Kalstone, Kalabhai Karlson Pvt. Ltd, India) and trimmed carefully to avoid deliberate posterior and lateral extension

loss. A wrought wire clasp was added in the areas that would not interfere with the occlusion of opposing teeth. Baseplate wax was adapted over the cast, and wax-up was done. This wax-up, along with cast was flasked, dewaxed in a conventional manner, and packed with heat cure acrylic resin (Trevalon, Dentsply, India) and cured. The palatal surface of a lid was made by adapting a sheet of cold-cure acrylic resin along the finish line seen on the obturator.

After finishing and polishing of obturator, it was delivered to the patient. The patient was instructed regarding the insertion and removal of the prosthesis and the maintenance of proper hygiene of both the defect and prosthesis. He was recalled after 24 hours following placement of the intermediate obturator to assess its function and examine the defect area for the early signs of irritation. Any necessary adjustments were made, and the patient was scheduled for the recall visits after one week for bite registration, followed by trying in for the missing teeth. Final wax-up of the obturator was done and which was followed by acrylization in heat cure polymer. The final obturator was finished, polished, and delivered to the patient, and aesthetic and functional rehabilitation was completed (Figure 4C,D&E).

## Discussion:

Mucormycosis is the third most prevalent opportunistic fungal infection, after Aspergillosis and Candidiasis, with high mortality and morbidity rate.<sup>10</sup> Mucoraceae is commonly present in soil and decaying food and infiltrates the body through inhalation, ingestion, or direct contamination of wounds. In a healthy individual with an active immune response, tissue macrophages phagocytose the inhaled spores and kill them.<sup>11</sup> If any spores escape the macrophages and germinate, the hyphae induce chemotaxis of neutrophils. The neutrophils produce reactive oxygen metabolites, perforin, cationic peptides, and enzymes and kill the spores and hyphae by oxidative cytotoxic effect.<sup>12</sup> However, in immunocompromised individuals, spores evade phagocytosis and germinate. The germlings express the spore coat homolog (CotH) proteins which bind to the receptor glucose-regulator protein 78 (GRP78) on the endothelial cells. The interaction and binding of CotH and GRP78 facilitate endocytosis of the fungus into the endothelial cell resulting in its damage.<sup>12</sup> Once fungus invades the arteries, it grows along the internal elastic lamina and causes vascular thrombosis and infarctions. The reduced blood supply results in the necrosis of the area supplied by the affected arteries and can lead to fungal osteomyelitis.<sup>13</sup>

Rapid diagnosis and initiation of therapy are critical due to the acute, fulminate nature of the infection. Diagnosis of Mucormycosis rests upon the clinical sign and symptoms, 3D imaging, and observation of fungal elements of specific morphology in biological specimens. Demonstration of hyphae under direct microscopic examination of specimens after treatment with potassium hydroxide (KOH) is a rapid and valuable method that highly suggests Mucormycosis.<sup>14</sup> A definitive diagnosis of Mucormycosis can be made by histopathological examination following hematoxylin and eosin (H&E), PAS, and GMS staining. In microscopic sections, mucormycosis appears as ribbon-like broad (4 to 20 pm), non-septate hyphae exhibiting obtuse or right-angle branching.<sup>15</sup> In our case the KOH treatment of pus was negative for mucormycosis, and the patient was initially treated for bacterial osteomyelitis using antimicrobial

medications. However, the identification of aseptate hyphae in the histopathologic examination of tissue resected during surgical debridement confirmed the diagnosis of mucormycosis.

The SARS-CoV-2 virus has been found to impair cell-mediated immunity due to decreased CD4+ and CD8+ cell counts, increasing the vulnerability to fungal infections.<sup>16</sup> Corticosteroids administered for COVID-19 management can increase blood sugar levels and ketoacidosis, encouraging the growth of Mucoraceae. Increased iron content and use of contaminated oxygen therapy equipment are considered additional risk factors for the development of mucormycosis in COVID-19 patients.<sup>17,18</sup> Furthermore, both non-humidified oxygen and steam-inhalation can lead to mucosal damage, facilitating Mucorales infection.<sup>19</sup> The patient had a history of severe COVID-19 and received corticosteroids and supportive oxygen therapy. Thus, the compromised immune response could have provided a favourable environment for the growth of Mucorales. The diagnosis of rhinocerebral mucormycosis suggests that fungus must have invaded the paranasal sinuses during the administration of supportive oxygen therapy or was present as normal commensal. The entry of fungal pathogen during extraction is unlikely as the patient already presented with initial manifestations of mucormycosis like toothache and mobility.

In the absence of any caries, crack, or history of dental trauma, the pulp necrosis of left maxillary incisors could be attributed to maxillary necrosis after thrombosis of the internal maxillary artery or descending palatine artery caused by mucormycotic infection.<sup>20</sup> This assumption could be corroborated with the histopathologic examination of dental pulp tissue where congested blood vessels with diffuse globular calcifications were observed. The management of Mucormycosis involves a combined approach of surgical debridement and systemic antifungals. In the present case, the necrotic bone was removed along with teeth involved in the pathology, and the patient was administered liposomal amphotericin B. Therefore, it can be highlighted that endodontic therapy must be performed after surgical intervention and can save the efforts of an endodontist, reduce the risk of introduction of infection during root canal treatment and minimize the patient discomfort.

The extensive and rapid spread of Mucormycosis makes it a life-threatening disease—aggressive surgical intervention results in significant aesthetic and functional deformity.<sup>21</sup> Prosthetic rehabilitation in patients with multiple facial defects is a daunting task. The prosthesis is essential in these cases because obturator prosthesis helps improve speech and mastication and reduce nasal regurgitation by extending into the defect and utilising undercuts to enhance retention and stability. It also improves the aesthetics by preventing the collapse of tissue and the replacement of missing teeth in the obturator.

## **Conclusion:**

The management of rhinocerebral mucormycosis requires a multidisciplinary approach. The dentist must be aware of the initial symptoms of Mucormycosis and should consult otorhinolaryngologists before any dental intervention, which can complicate the treatment.

## **Declarations**

## **Conflict of interest statement:**

The authors declare that there is no conflict of interest.

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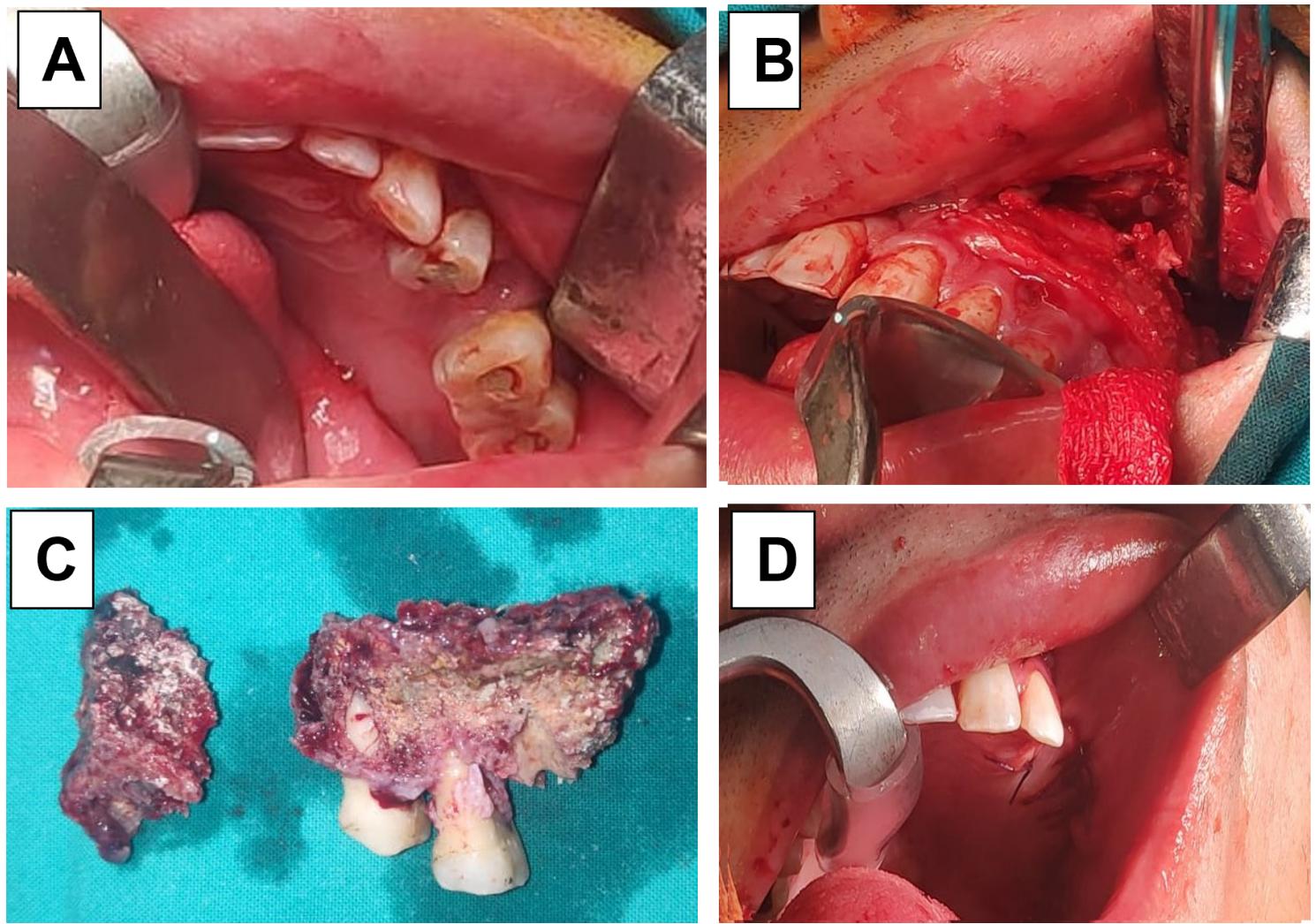
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## Figures



**Figure 1**

**Figure 1(A to E):** CECT scan of the face: A)The bony window showing Soft tissue density involving left maxillary sinus with the erosion of maxilla and zygoma, with loss of retroantral fat B) CECT showing soft tissue density involving left maxillary sinus with loss of retroantral fat and soft tissue density lesion involving left retroantral and premaxillary region. C) shows osteomyelitic changes in upper alveolus D) shows residual Soft tissue density lesion in left maxillary sinus with osteomyelitic changes involving maxilla and zygoma(post 1<sup>st</sup> debridement) E)showing palatal defect following debridement



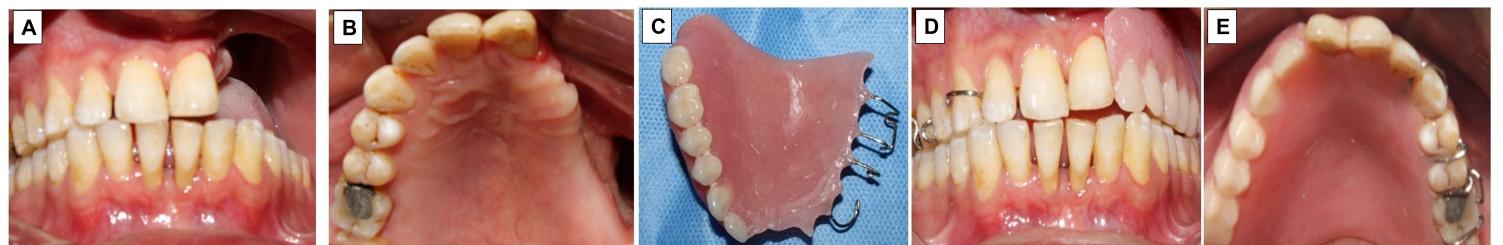
**Figure 2**

**Figure 2:** (A) preoperative intraoral clinical picture (B) intraoperative picture (C) excised necrotic bone segment with teeth (D) approximation of the surgical site with sutures.



**Figure 3**

**Figure 3:**(A)Preoperative radiograph showing diffuse periapical radiolucency around tooth #21 & 22. (B) postoperative radiograph after completion of root canal treatment of tooth #21 & 22. (C) Histopathology displaying necrotic pulp with fibrotic changes, basophilic calcifications, peripheral retraction from the stroma (red arrow), congested blood vessels (inset showing 4X magnification).



**Figure 4**

**Figure 4:** (A&B)Intraoral photograph after second surgical procedure. (C,D&E) Functional and aesthetic rehabilitation by obturator prosthesis