

COVID-19-associated mucormycosis involving the maxilla

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Abstract

It is important to increase the awareness of head and neck surgeons about the recent surge of craniofacial mucormycosis in COVID-19 patients, because early diagnosis and treatment are essential to improve the outcomes. Here, we describe clinical features, treatment protocols, and outcomes of treatment in 8 patients with COVID-19-associated mucormycosis

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It is important to increase the awareness and knowledge of head and neck surgeons about the recent surge of craniofacial mucormycosis in COVID-19 patients, because early diagnosis and appropriate treatment are essential to improve the outcomes. Here, we describe clinical features, treatment protocols, and outcomes of treatment in 8 patients with COVID-19-associated mucormycosis in the maxilla. Consistent with the findings of previous studies, our experience in the management of these 8 patients shows that early administration of amphotericin B and prompt aggressive surgery are essential for optimal control of the disease.

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a virus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The virus causes infection in the lower respiratory tract, potentially leading to diffuse alveolar damage, acute respiratory distress syndrome, and ground-glass opacification of the lungs. Due to a severe systemic inflammatory reaction, COVID-19 alters the cell-mediated immune response by decreasing the number of T-lymphocytes, especially the cytotoxic and helper T cells. This makes the patient susceptible to a wide range of super-infections, particularly fungal infections.¹

Mucormycosis is an acute and rapidly progressing infection caused by a family of fungi called mucoromycetes. The family includes many different species of fungi including *Rhizopus*, *Mucor*, *Lichtheimia*, etc. The *Rhizopus* is the most common type and responsible for nearly 60% of mucormycosis cases in humans.² Mucormycosis mostly involves head and neck area and begins when fungal spores reach the paranasal sinuses by means of inhalation, and spread into adjacent structures including the maxillary bone, the orbital cavity, and the cranium.³ A correct diagnosis of mucormycosis depends on histopathologic examination of tissue samples and detection of the hyphae of the Mucorales in the specimens.

Before the COVID-19 outbreak, mucormycosis was limited to patients with decreased immunity due to uncontrolled diabetes, end-stage renal failure, organ transplantation, and hematological malignancies. A few months after the outbreak of COVID-19, many case reports have described cranio-maxillofacial mucormycosis associated with the disease.⁴ It seems that both COVID-19 itself and medications that are used for the management of COVID-19 are responsible for underlying conditions that promote the germination of

spores in tissues. These conditions include hypoxia due to lung damage, a decline in the number and activity of white blood cells, steroid-induced hyperglycemia and immunosuppression, acidic medium created by metabolic acidosis, and high ferritin levels due to inflammation. Among these conditions, immunosuppression is probably the most important contributing factor. Studies have demonstrated that there is a more intense level of lymphocytopenia in severe COVID-19 compared to mild disease.⁵ Furthermore, high doses of corticosteroids are commonly prescribed as a life-saving measure in patients with severe COVID-19.⁶ Corticosteroids suppress the immune system by decreasing the number of cytotoxic and helper T cells. In this way, corticosteroids fight against severe inflammation caused by the virus, but create a favorable environment for other opportunistic infections. Therefore, administration of corticosteroids makes the immunocompromised COVID-19 patients even more susceptible to fungal co-infections.

Case report

In 2021, during a period of 4 months, we admitted and treated 8 patients with COVID-19-associated mucormycosis in the Shariati hospital in Tehran, Iran. All patients had been previously hospitalized and had received intravenous corticosteroids for the management of severe COVID-19 pneumonia. They had been discharged with stable conditions before being admitted to our department for the management of mucormycosis in the upper jaw. The mean time interval between the diagnosis of COVID-19 and admission to our department for the management of mucormycosis was 41 days. All patients initially presented with acute maxillary sinusitis as well as pain and tooth mobility in the upper jaw. Six patients had necrotic bone exposure intraorally (Fig. 1). In all patients, computed tomography (CT) scans revealed involvement of the maxillary sinus and partial destruction of the maxillary bone (Figure 2). Table 1 summarizes demographic as well as clinical findings in these 8 patients.

All patients underwent aggressive surgery to remove hopeless teeth, necrotic bone and pathologic tissues. Tissue specimens were submitted for histopathologic evaluation. Microscopic evaluation revealed the presence of rectangular-shaped aseptate hyphae in the specimens, confirming the diagnosis of mucormycosis. In addition to surgical intervention, all patients received intravenous amphotericin B (5 mg/kg/day) during hospitalization.

Discussion

A study of 101 patients with COVID-19-associated mucormycosis found that 80% of patients had diabetes mellitus and 76% had taken steroids for the management of COVID-19.⁷ It seems that COVID-19 is potentially a diabetogenic disease. Of note, the SARS-CoV-2 can directly damage the pancreatic cells and impede insulin secretion, leading to acute diabetes and ketoacidosis.^{8,9} In most hospital centers, steroids are widely used in the management of severe cases of COVID-19. This has been proved to be effective in reducing mortality and hospital stay,¹⁰ but the immunosuppressive and diabetogenic effects of steroids may increase the risk of developing mucormycosis in these patients.

All our patients were successfully recovered from COVID-19 but developed craniofacial mucormycosis shortly after recovery. All had diabetes and had received corticosteroids for the management of COVID-19. On the basis of our experience, we recommend that intraoral examination should become a routine part of medical examination in patients who have COVID-19 or have recently recovered from the disease. This could lead to early diagnosis of mucormycosis and a significant reduction in the rate of mortality and morbidity associated with the disease.

In a study of 167 patients with COVID-19-associated mucormycosis, the overall mortality rate was found to be 38%.¹¹ Furthermore, the study showed that survival rate was higher in patients who underwent both medical and surgical management (65%) compared to patients who received medical management only (22%).

Effective management of COVID-19-associated mucormycosis requires a multidisciplinary approach involving several specialties including ear-nose-throat (ENT) surgeons, infectious disease specialists, endocrinologist, and maxillofacial surgeons. A timely combination of surgical debridement and antifungal therapy is mandatory to control the disease.

Owing to the high morbidity and mortality of COVID-19-associated mucormycosis, even the slightest clinical suspicion warrants initiation of antifungal therapy. Amphotericin B should be started as soon as possible and continued until improvement is evident both in clinical examinations and in follow-up CT scans. In our experience, antifungal therapy will be necessary for just a few weeks if adequate and prompt surgical debridement is performed.

Mucormycosis is an angio-invasive disease which destructs blood vessels and causes thrombosis, leading to poor tissue perfusion. This, in turn, gives rise to poor drug bioavailability to the infection site, which makes antifungal therapy progressively less effective. This vicious cycle could be broken only by aggressive surgery in the earliest possible time. Therefore, the role of surgical debridement in the management of COVID-19 associated mucormycosis cannot be overemphasized.

Conflict of interests

The authors have none.

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Figures and table:

Figure 1: Exposure of necrotic maxillary bone in a patient with COVID-19-associated mucormycosis

Figure 2: Axial CT scan of the maxilla in a patient with COVID-19-associated mucormycosis. Bone destruction is evident in the left hemi-maxilla, involving both the alveolar bone and the basal bone.

Table 1: Demographic and clinical findings in 8 patients with COVID-19-associated mucormycosis

	Gender	Age	Comorbidities	Medications for COVID-19 management	Numbness in midface	Necrotic bone exposure
1	Male	38	Diabetes mellitus	Dexamethasone	Yes	Yes
2	Male	55	Diabetes mellitus	Dexamethasone & Remdesivir	No	Yes
3	Male	50	Diabetes mellitus	Dexamethasone	No	Yes
4	Male	41	Diabetes mellitus	Dexamethasone & Remdesivir	Yes	Yes
5	Female	68	Diabetes mellitus	Dexamethasone	Yes	No
6	Male	44	Diabetes mellitus	Dexamethasone & Remdesivir	Yes	Yes
7	Female	58	Diabetes mellitus	Dexamethasone & Remdesivir	No	No
8	Male	61	Diabetes mellitus	Dexamethasone	Yes	Yes





