

Mucormycosis - Case series on uninvited resident evil in COVID-19 patients

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Case Report

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ABSTRACT

Mucormycosis is an aggressive opportunistic infection ascribed to the inhalation of fungal spores which, normally infect the nose and paranasal sinuses. This fulminant form commonly infects immunosuppressed human hosts, especially patients with AIDS, poorly controlled diabetes, lymphoma, leukemia, and those on long-term steroid use. The rise in patients with rhino-orbital mucormycosis associated with COVID-19 created havoc in this pandemic season. In this article, six cases of Covid-19 associated Mucormycosis are reported. The timely diagnosis and appropriate management of this deadly invasive disease can help to reduce the mortality and morbidity rate. Some healthy individuals too developed Mucormycosis (phycomycosis, zygomycosis) even when no risk factors were identified. Air conditioning can cause mucosal epithelium dryness, providing an optimal habitat for this organism to grow and multiply, thus leading to Mucormycosis. The global fatality rate for mucormycosis is 46%. Early diagnosis and therapy are crucial because mucormycosis has poor prognosis. The diagnosis of mucormycosis depends on pathological findings, clinical features, and imaging, which plays a crucial role in defining the extent of the invasiveness.

Key Words: Corticosteroids, Covid-19, diabetes mellitus (T2DM), immunosuppression, mucormycosis.

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INTRODUCTION

Coronavirus (SARS-CoV-2) or Covid 19 is associated with a respiratory illness resulting in severe pneumonia from acute respiratory distress syndrome (ARDS). The main fungal pathogenic culprits in COVID-19 patients were reported to be *Aspergillus* and *Candida*. The primary facilitators for these fungal spore germination in COVID-19 infected people are hypoxic surroundings, excessive blood glucose, surplus iron levels, and downplay of white blood cells (WBC) due to immunosuppression, extended hospitalization with or without the use of mechanical ventilators. Some healthy individuals too developed Mucormycosis (phycomycosis, zygomycosis) even when no risk factors were identified. Air conditioning can cause mucosal epithelium dryness, providing an optimal habitat for this organism to grow and multiply, thus leading to Mucormycosis^[1].

Mucormycosis is an uncommon opportunistic infection caused by fungi belonging to the Mucoraceae family of

which *Rhizopus oryzae* being the most common offender. After candidiasis and aspergillosis, the third most common angioinvasive mycotic infection is mucormycosis. Mucormycosis infection occurs in the compromised host because of impaired immunity, resulting in rapid proliferation and invasion of fungal organisms in deeper tissues^[2]. Although mucormycosis affecting the maxilla is rare due to the strong blood vascular supply in the maxillofacial areas, highly virulent fungi can cause fatal mucormycosis. Even by inhalation, the fungus can migrate from paranasal sinuses to orbit then to the meninges and finally to the brain. The most infected area is the rhinomaxillary site. Early diagnosis of the disease and prompt medical and surgical interventions are needed to reduce the mortality and morbidity associated with the disease^[3].

Despite enormous efforts, there is no accurate approved treatment for Covid 19. The best options are precautionary and symptomatic management. Secondary infections are commonly reported in severely ill Corona

patients. As the pathophysiology of Covid 19 is not yet fully understood, it cannot be determined whether Mucormycosis is a complication in the treatment of covid or by the disease itself⁴¹. Highly potent corticosteroids are observed to reduce lung injury due to inflammation and progression of respiratory failure in Covid-19 by producing immunosuppression, which may lead to secondary infections, precipitate latent diabetes mellitus, mood swings, weight gain, sleep disorders, myalgia etc. Globally 0.005 to 1.7 per million suffered from mucormycosis in Covid 19 till now. The incidence of mucormycosis is 0.14 per 1000 in the Indian population, (80 times more than in developed countries). The global fatality rate for mucormycosis is 46%. Early diagnosis and therapy are crucial because mucormycosis has poor prognosis⁵¹.

CASE REPORT:

Case Report 1:

A 44-year male came to ophthalmology OPD with complaints of pain and inflammation in the right eye. Upper maxillary tooth extraction was carried out 4 months ago due to local infection and inflammation. The medical history revealed that he had been on medication for four months for uncontrolled diabetes mellitus and had low hemoglobin levels. He incidentally tested positive for COVID-19. A preliminary diagnosis of mucormycosis of the maxilla was determined based on the history and clinical features. The conclusive diagnosis of mucormycosis of the maxilla was made by histopathological examination. The maxilla was then surgically removed. After a year of follow-up, there was no sign of recurrence. (Fig. 1)

Case Report 2:

A 38-year-old man was admitted with high-grade fever, body pains and cough for the past 4 days. He tested positive for COVID-19. As part of the initial management of COVID-19, he was given methylprednisolone infusion for 18 days, IV Remdesivir in a Stat dose of 200 mg followed by 100 mg OD for 11 days, and injection of Dexamethasone 4 mg BD for 12 days. The patient complained of pain and swelling in the right eye after 18 days. Mucormycosis was validated by histopathology analysis, identified Gram positive bacilli, and broad-based aseptate hyphae. Tobramycin eye drops BD, 300 mg of Amphotericin B per day and Nepafenac ophthalmic suspension 3 times a day were some of the medications recommended. The patient recovered in 25 days. (Fig. 2)

Case Report 3:

A 50-year female presented with dry cough, myalgia, shortness of breath and fatigue for past 3 days. Her medical history disclosed T2DM and hypertension (HTN) for last five years. She was diagnosed with Covid 19 using reverse-

transcription polymerase chain reaction (RT-PCR). During hospitalization, patient received Remdesivir injections (200 mg on first day of admission and 100 mg on days 2–5) and dexamethasone (6 mg OD for 10 days). The patient was discharged after 21 days with a significant clinical improvement. On the fifth day after discharge, the patient was readmitted due to swelling, numbness, and erythema, which were prominent on the left side of the face. Histopathological examination of necrotic and suppurative tissue biopsies showed broad, pauciseptate hyphae that confirmed mucormycosis as diagnosis. During her stay in the hospital, she received IV liposomal amphotericin B. She was discharged finally after 28 days with significant reduction in swelling and erythema.

Case Report 4:

A woman of 40 years, diagnosed with diabetes mellitus presented pain in the face for 5 days without additional symptoms. Tenderness of the sinuses on the left side of the face, necrotic eschars on the palate were detected during clinical examination. The left eye was completely paralyzed with no direct light reflex, but the movements and vision of the right eye were normal. She tested positive for COVID-19 by RT-PCR on day 2 of hospitalization. Histopathological analysis of the ethmoid sinus biopsy revealed broad aseptate hyphae that confirmed diagnosis as mucormycosis. The patient received conventional amphotericin B for 11 days after which radiological examination revealed a reduction in sinus opacification. (Fig. 3)

Case Report 5:

A 47-year-old male patient with past history of diabetes mellitus (DM), hypertension (HTN), was treated in another tertiary care centre for moderate COVID-19 pneumonia and uncontrolled T2DM and presented to emergency department with swelling in his right eye and a black-colored lesion on his right cheek on day 3. His treatment included Meropenem, Remdesivir, and fluconazole injections and was referred to the emergency department for further treatment. The acute history, the findings of physical examination, the history of long-standing diabetes along with COVID-19, and the identification of fungal smear and cultures established a working diagnosis of mucormycosis. The patient was administered Vancomycin, Amphotericin B, and Meropenem intravenously. He was discharged 3 weeks after recovery. (Fig. 4)

Case Report 6:

A 57-year-old male patient with no underlying risk factors was admitted to the hospital with dyspnoea, cough, and saturation of 73%. Results of chest radiograph (CXR), lung CT, and RT-PCR showed a definitive diagnosis of COVID-19. He was treated with Remdesivir 250 mg Stat

dose and then 100 mg daily, methyl prednisolone 250 mg on day 1 and then 125 mg for 3 days. He was discharged in good condition after ten days. The patient was readmitted after 4 days of discharge due to nasal obstruction and orbital swelling on the right side of the face. Since the clinical presentation confirmed the possibility of mucormycosis, IV amphotericin B was started at 3 mg/kg/day. Due to massive invasiveness into the cheeks and orbit, unfortunately the patient expired on the 11th day of readmission (Fig. 5).

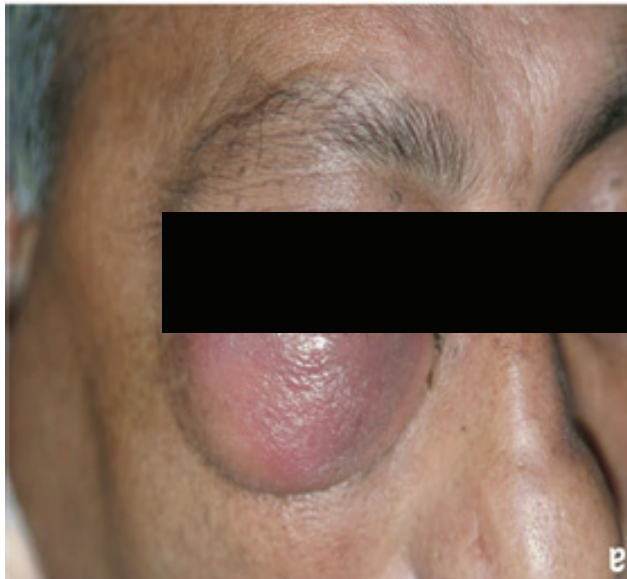


Fig 1: Case report 1, Patient with facial swelling, periorbital edema, and erythema



Fig 2: Case report 2, Patient presented with right total ophthalmoplegia



Fig 3: Case report 4, Patient with necrotic eschars on the palate



Fig 4: Case report 5, Right eye swelling and black eschar on the right cheek



Fig 5: Case report 6, Right side of the patient’s face shows an extensive fungal lesion

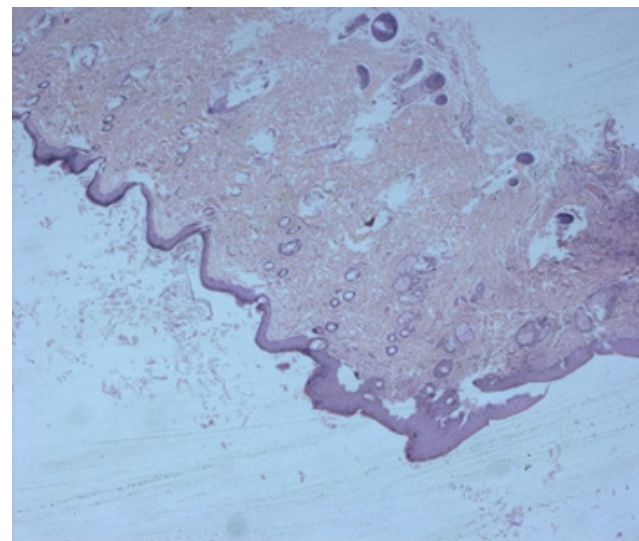


Fig 8: Complete re-epithelization of wound region in epidermis with normal morphology of skin

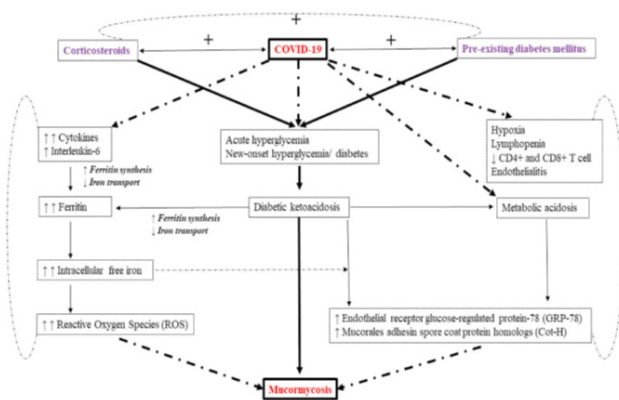


Fig 6: Interaction of diabetes, corticosteroid and COVID-19 with Mucormycosis

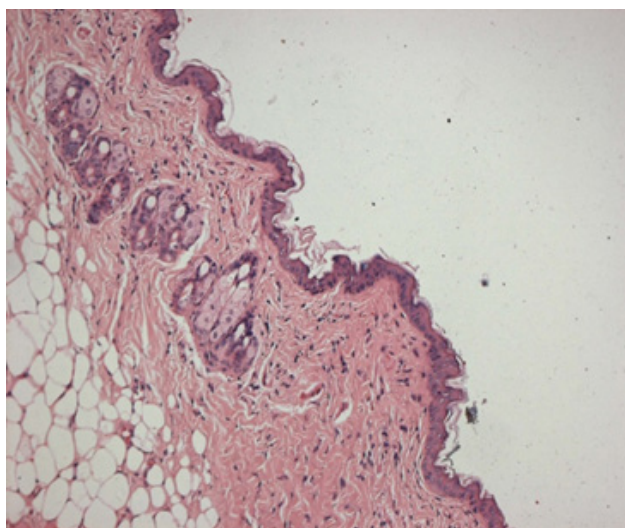


Fig 7: Epidermal layer with hyperplasia with dermal inflammation

DISCUSSION

Coinfections with Covid 19 can occur when there is immune dysregulation with a reduction in T cell count, CD4, CD8 T cells and a sharp shoot in the interleukin (IL)-2, IL-10, IL-6 and TNF- α values, thus adversely affecting the prognosis of the disease^[6]. Angioinvasion is the hallmark of mucormycosis that leads to thrombosis, infarction, and tissue necrosis. Uncontrolled diabetes, malignancies such as lymphomas and leukemia, renal failure, long-term immunosuppressive therapy, burns, protein-energy malnutrition, and AIDS are the predisposing factors for Mucormycosis^[7]. The diagnosis of mucormycosis depends on pathological findings, clinical features, and imaging, which plays a crucial role in defining the extent of the invasiveness.

Mucormycosis of the oral cavity has two causes. One is caused by disseminated infection, with inhalation through the nose, and the other is caused by direct wound contamination, as a result of which it also spreads to other visceral organs. If it spreads through the inhalational route, the infection can cause palatal ulceration, leading to necrosis in most of the cases^[8].

Diabetes mellitus alters the normal immune response of the body in a variety of ways. Hyperglycemia increases the proliferation of fungal organisms. *Rhizopus oryzae*, is the common cause of rhinomaxillary mucormycosis in diabetic ketoacidosis patients because these organisms use ketone bodies in the body through the ketoreductase enzyme. It has been stated that diabetic ketoacidosis alters transferrin's ability to temporarily bind to iron, which

in turn disrupts the critical host defense mechanism and allows *Rhizopus oryzae* to proliferate inside body^[9].

The interaction of T2DM, corticosteroid and COVID-19 with mucormycosis is explained in Fig.^[6]

The mainstay of the diagnosis of mucormycosis is histopathological examination. The diagnosis is confirmed by spotting broad ribbon-shaped hyphae (10 to 20 micrometres) invading blood vessels. The morphology, breadth, branching angle, and septation should all be analyzed under the microscope. In some patients, even aspergillus has the potential to be pathogenic. For exact confirmation, tissue biopsy sample cultures should be done. Because of slow growth of these fungi in cultures, these tests are sometimes not clinically relevant because the patient may pass away from the infection long before the cultures have been obtained.

As a result, mucormycosis and aspergillosis can be distinguished using histopathological methods. Depending on the anatomical location, numerous biopsy methods can be used. The most common place for a biopsy is the paranasal sinuses, and endoscopic method can be used. Although interventional radiological approaches may also be useful for other anatomical locations such as the lungs, gastrointestinal tract, etc., these may need more invasive endoscopic procedures to retrieve tissue for histology. In particular, the absence of hyphae should not prevent the diagnosis from being made because risk factors and clinical findings may point to this infection and treatment has to be prompt even in such cases.

Broad aseptate fungal hyphae with right-angle branching are visible in the histopathological lesion. In the present case, the same histopathology was revealed. Aspergillosis with narrow septate hyphae is one of the histopathological differential diagnosis.

The primary goal is to treat the underlying causative factor of the disease. Once the diagnosis is established, the patient received only conservative treatment. IV Amphotericin B and surgical debridement are the two mainstays of treatment. Amphotericin B is a fungistatic agent, which halts progression of disease^[10].

CONCLUSION

The exact origin and cause of mucormycosis in patients of COVID-19 is not yet fully understood. Appropriate treatment guidelines along with rational use of corticosteroids need to be re-evaluated and specific recommendations should be established in order to reduce mortality and morbidity. Timely diagnosis, suitable antifungal treatment (the most common being amphotericin

B) with surgical debridement of the affected area is a very essential element in the management of Mucormycosis^[11]. Necessary precautions should be taken to maintain optimal glucose level; corticosteroids should be used judiciously in corona patients.

CONFLICT OF INTEREST

There are no conflicts of interest.

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