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Mucormycosis in Covid-19 Era: A Detailed Case Report

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We report a case of Covid-19 era Mucormycosis infection involving the maxilla caused by an aseptate fungal hyphae along with its management. The patient was diagnosed based on clinical features, radiological imaging and biopsy reports as fungal osteomyelitis (Mucormycosis). The patient was advised for surgical resection of the lesion along with the surgical debridement under general anesthesia. In head and neck cases, the mold usually gains entry through the respiratory tract involving the nose and sinuses with further progression into orbital and intracranial structures. Hence, an early and prompt diagnosis along with the intervention is required for a good prognosis, and decreasing morbidity. This can be achieved based on clinical pictures, radiological evaluation and various smears.

1. Introduction

Zygomycetes comprise Mucorales and entomothorales.[1] The former order causes life-threatening fungal infections, and mucormycosis mainly in immunocompromised hosts while the latter order causes superficial and mucocutaneous infections in immunocompetent hosts. Among Mucoraceae, Rhizopus Oryzae is the most common cause of infection.[2] Phagocytes are the major host defense mechanism against Mucormycosis. A hallmark of mucormycosis

infection is the presence of extensive angioinvasion with resultant vessel thrombosis and tissue necrosis. The infection mainly affects the brain, sinuses, and lungs. The various forms of mucormycosis include disseminated, rhinocerebral, pulmonary, cutaneous and renal Mucormycosis.[3] The most vulnerable population affected with fungal infections are steroid using patients, diabetic patients, immunocompromised patients, patients with hematological malignancies, and solid organ transplant patients. This case report describes the clinico-etiopathogenesis of mucormycosis as well as the role of imaging and management of this dreadful entity.

2. CASE REPORT

A 69 -year- old male patient presented with a complaint of swelling on the right side of the face for 15-20 days The patient was relatively asymptomatic 2 months back when he experienced fever for which he was hospitalized & the fever subsided after 5 days. Further, the patient started noticing pain in the nose, more on the right side following which he noticed bleeding from the right nostril while cleaning the nose. Subsequently he developed pain in the right side of the upper tooth region after 4-5 days and gave a history of tooth extraction in the upper right back tooth region in a private dental clinic. After extraction socket did not heal and pain aggravated further. He was referred to Subharti dental college & hospital, Meerut for further evaluation & management. Medical history of the patient revealed that he was a known diabetic from past 2 years & suffered from tuberculosis 15 years earlier. The patient had a habit of smoking 3-4 bidis/day for 20 yrs.

CLINICAL PRESENTATION

Extraoral examination showed mild facial asymmetry with diffuse swelling extending mediolaterally from the ala of the nose to the malar region on the right side & superior-inferiorly from the infraorbital region to 1cm below the angle of mouth (Figure 1).. Tenderness was present over the right cheek, malar & ala of the nose region. Submandibular lymph nodes on the right side were palpable & tender.

Figure 1: Extraoral Frontal View showing mild swelling

Intraoral examination showed an oval-shaped swelling with an abscess measuring about 1x1 cm in size noticed in the mid palatal region(Figure 2). The swelling was soft & fluctuant inconsistently, with overlying mucosa which was slightly red, and the swelling was tender on palpation with pus discharge. There were multiple gingival abscesses & a nonhealing extraction socket seen in the right maxillary 1st molar region. Multiple mobile teeth with grade I mobility were seen in the anterior maxillary region. Segmental mobility was also evident in maxillary right central incisor to 2nd premolar and left central incisor to canine region.

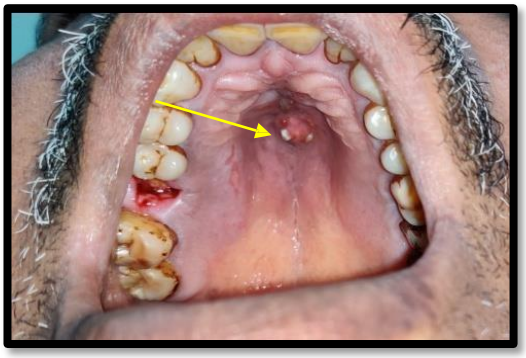


Figure 2: Intraoral Palatal lesion showing abscess formation with pus discharge (Yellow arrow showing the lesion).

Radiologic examination with Contrast-Enhanced Computed Tomography (CECT) report showed haziness over the right maxillary sinus and also sinus mucosal thickening was seen in the maxillary sinus bilaterally(Figure 3A-C).

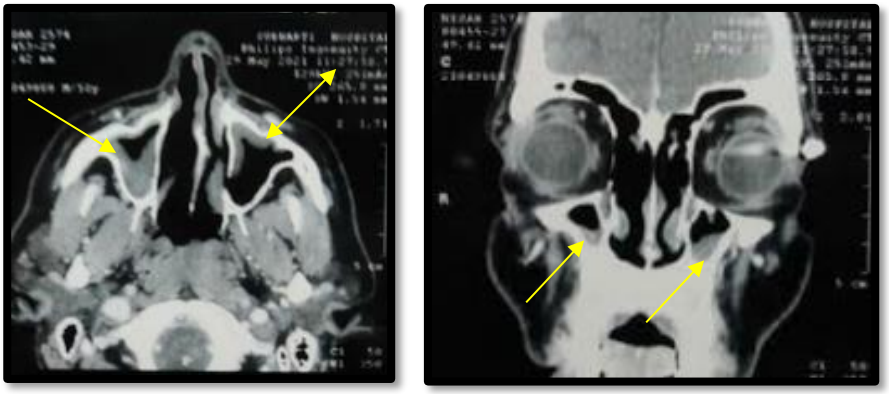


Figure3:3A: Axial View showing bilateral maxillary sinus mucosal thickening (Yellow arrow). 3B: Coronal View showing bilateral maxillary sinus mucosal thickening (Yellow arrow).

3C: Sagittal View showing bilateral maxillary sinus mucosal thickening (Yellow arrow).

Investigation showed negative KOH mount (Nasal and oral), negative RTPCR, negative viral markers (HIV,HCV,HBsAg). Plasma glucose level was found to be 258mg/dL and HbA1c was 11.5%.

Based on clinical findings of palatal swelling with abscess, history of nasal discharge (nasal bleeding from right nostril), the segmental mobility of anterior maxilla & medical history of diabetes mellitus. Mucormycosis was given as a provisional diagnosis.

Based on the patient past history of fever, diabetes & tuberculosis (15 years back), nasal bleeding, swelling and important clinical features of abscess on the mid-palate, toothache, and multiple tooth mobility following differential diagnosis were considered:

1. Fungal osteomyelitis (Mucormycosis)
2. Tubercular osteomyelitis
3. Maxillary sinus malignancy
4. Minor salivary gland tumor
5. Necrotizing sailometaplasia

Figure 4: Incisional Biopsy along with the necrotic bone

Incisional biopsy of the mid-palatal region was performed (Figure 4). Microscopically lesions revealed hyperplastic stratified squamous epithelium, with underlying inflamed connective tissue stroma, showing collagen fibers, fibroblast, chronic inflammatory cells, predominantly lymphocytes. Large hemorrhagic areas were also seen. Few fungal elements were seen throughout the section and decalcified section showed non vital bony trabeculae devoid of osteocytes. The fungi were thin walled, ribbon like hyphae without septation branching at right angle. So, the final diagnosis was given as fungal osteomyelitis probably Mucormycosis. The patient was advised culture for confirmatory diagnosis.

Based on clinical features, radiological evaluation and biopsy report the patient was advised for surgical treatment in which partial maxillectomy of right side & palatectomy along with surgical debridement of the lesion were performed (Figure 5).

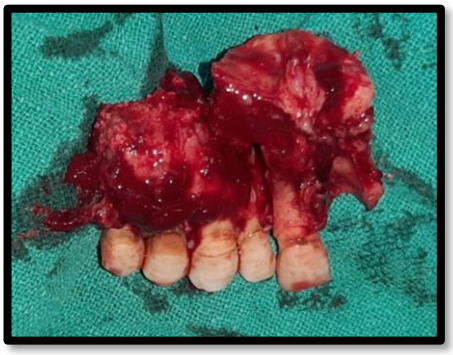
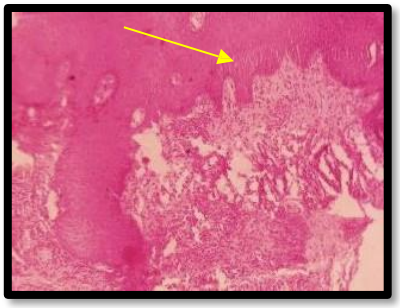


Figure 5: Excisional Biopsy (Partial maxillectomy along with palatectomy)

Then after the surgical procedure, the resected specimen was sent to the histopathological evaluation for further confirmation of the lesion. Excisional biopsy was also suggestive of aseptate branching fungal hyphae (Figure 9) morphologically consistent with Mucormycosis with associated granulomatous inflammation (Figure 7), osteomyelitis and sinusitis. The patient was kept on follow-up and was advised for prosthetic rehabilitation after 6 months of surgery (Figure 10).



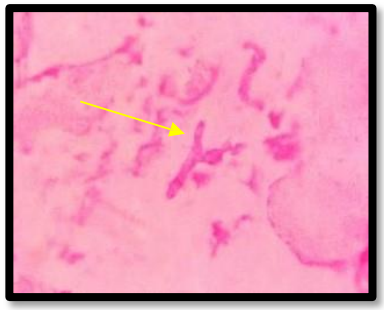


Figure 7: Histopathological section Figure 9: Histopathological section showing fungal hyphae showing hyperplastic Stratified squamous epithelium

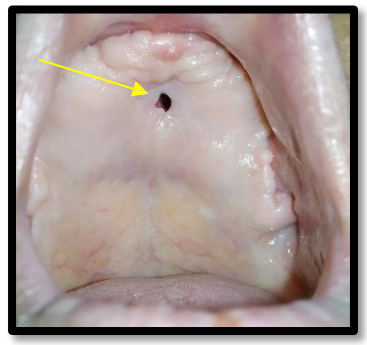


Figure 10: Post operative 3 months followup showing fistula formation in palatal region.

3. DISCUSSION

In past two years we have encountered one of the most important as well as life-threatening complications of Covid-19 infection i.e; Mucormycosis. Mucormycosis is often referred to as the 'Black fungus'. This is a misnomer. Mucor is not a black fungus. The black fungus often called Dematecious fungi, or pigmented fungi is a completely different family. Technically, Mucor is not a black fungus, it causes the tissue affected to necrose and turn black. Mucormycosis is an aggressive, deadly angio-invasive fungal disease caused by the ubiquitous filamentous fungi of the order Mucorales & belonging to the class of Zygomycetes.

Furbinger[4] described the first case in 1876 in Germany when he had found a patient who died of cancer and the right lung of the patient had shown fungal sporangia and hyphae into a hemorrhagic infarct (Figure 6). The first case of the disseminated type of mucormycosis was published by Arnold Paltauf in 1885.[5] Paltauf, the German pathologist named the condition "Mycosis mucorina".[6] Baker, an American pathologist, coined the term Mucormycosis.[5]

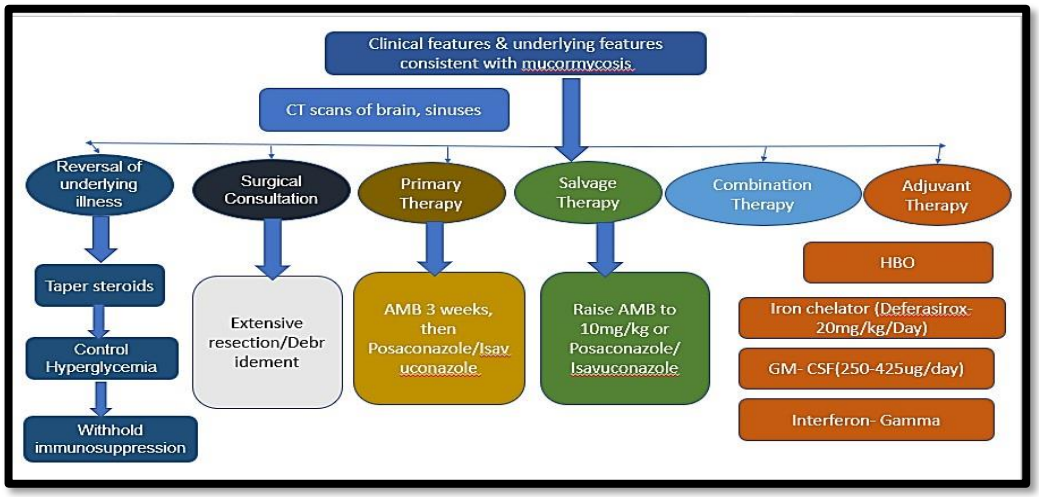


Figure 6: Concise outline of Mucormycosis treatment

*Chakrabarti A, Singh S. Management of Mucormycosis. Current Fungal Infection Reports.2020 Dec;14(4):348-60.

The prevalence of mucormycosis in India is reported to be approximately 0.14 cases per 1000 population, which is about 80 times the prevalence reported in other developed countries. Depending on the site of infection and underlying predisposing factors, cross-sectional may vary from 40%- 80%.[7]

The appearance of widespread angioinvasion, with resulting vascular thrombosis and tissue necrosis, is a trademark of mucormycosis infections. The ability of the organism to hematogenously diffuse from the original site of infection to other target organs is linked to angioinvasion (Figure 8). As a result, endothelial cell destruction and penetration via blood arteries is likely a vital phase in the organism's pathogenetic approach.[8]

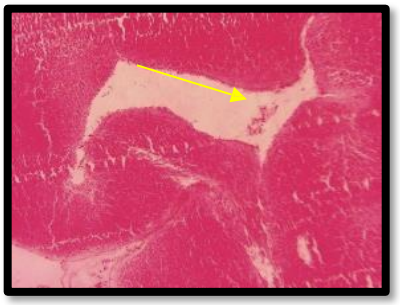


Figure 8: Histopathological section showing large Haemorrhagic areas

Increased blood iron is a risk factor for mucormycosis because iron plays an important role in the infection's aetiology. Iron is linked to transferrin and ferritin in normal hosts and not available to Mucorales fungus, but in vulnerable hosts such as Diabetic ketoacidosis (DKA), Diabetes Mellitus (DM), and others, transferrin's ability to bind to iron is reduced, resulting in a rise in serum iron level.[9]

Three ways of acquiring iron are:

1. From diabetes mellitus or diabetic ketoacidosis (DKA) host-

Mucorales have virulence factors, which allow them to cause disease. The ability to obtain iron from the host is one such characteristic. Iron is a critical component of cell growth and development, as well as a number of critical cell activities. As a result, viruses that are successful use a variety of methods to extract iron from their hosts. Recent research shows that the amount of accessible, unbound iron in the blood plays a key role in predisposing people with DKA to mucormycosis. Iron is coupled to host carrier proteins such as transferrin, ferritin, and lactoferrin in mammalian hosts. The harmful effect of free iron is avoided by this sequestration. Because R. oryzae is a member of the Mucorales, this strategy of reducing iron availability is a major universal host defence mechanism against microorganisms in general and Mucorales in particular. The clinical fact that patients with DKA are particularly prone to mucormycosis supports the theory that iron absorption plays a role in the disease's aetiology.

2. From siderophores released by fungi-

By acting as a xenosiderophore, the bacterial siderophore deferoxamine predisposes people to Rhizopus infection. Rhizopus is reported to secrete rhizoferrin, a polycarboxylate siderophore. Rhizopus receives iron from this siderophore via a receptor-mediated, energy-dependent mechanism. In this regard, the genome-sequencing study of R. oryzae found 13 potential siderophore permeases, including rhizoferrin and deferoxamine, that could operate as siderophore receptors. However, it is unclear whether rhizoferrin transfers iron by releasing iron extracellularly or by first internalising the siderophore and then releasing iron in the cytoplasm. Because rhizoferrin is ineffective at getting iron from serum, the contribution of the organism's endogenous siderophores to its pathogenicity in a mammalian host is expected to be small.

3. Through heme-

The utilisation of heme by fungi to get iron from the host is a third mechanism. The Rhizopus genome project identified two heme oxygenase homologues . These two R. oryzae homologues may allow R. oryzae to get iron from the host's haemoglobin, which could explain R. Oryzae's angioinvasive nature.[8.9]

The commonest clinical feature at presentation is a nasal block, ocular pain, or swelling of the lid. Apart from these, rare presentations like the sudden loss of vision are also seen as presenting features. Nearly 53.7% of ROCM cases are associated with a significant loss of vision. Regarding rhino-nasal involvement, 2 studies reported nasal blockage as presenting symptom in their study population (11.8%). 6 studies reported palatal involvement as presenting feature in their study population (35.6%).[10] Sarkar et al[11] reported an incidence of 6 in 10 cases of central retinal artery occlusion in their study and all were unilateral.

Pakdel et al[12] conducted a cross-sectional descriptive multicenter study from Iran and concluded that clinicians should be aware that mucormycosis may be a complication of COVID-19 in high-risk patients. Poor control of diabetes mellitus is an important predisposing factor for complementary and alternative medicine (CAM). Rajalingam[13] in 2022 conducted a study on imaging in mucormycosis that concluded imaging helped in early diagnosis, assessment of disease extent, surgical planning and follow-up evaluation. Both Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) were helpful tests but MRI gave a better resolution of the soft tissue. It detected invasion of orbital soft tissue, infratemporal fossa, intracranial structures, perineural tissue cavernous sinus involvement and vascular occlusion. Sharma et al[14] reported the involvement of the ethmoid sinus is the most common involved paranasal sinus (100%) among the included patients.

Rabagliati et al[15] in their retrospective study of 16 non-immunocompromised adults (all admitted to intensive care unit [ICU]) reported 1 ROCM case (causative agent being R. microspore) and the risk factor was uncontrolled Diabetes Mellitus. Moorthy et al[16] in their retrospective observational multi-centric study explored the relationship between SARS-CoV-2 and probable risk factors. They concluded that there was a significantly higher incidence of diabetes amongst the patients who were COVID-19 positive with mucormycosis. Sharma et al[17] noted that there was one patient with renal failure at the time of presentation of mucormycosis out of 23 patients and thought renal failure might be another association or risk

factor of occurrence of Mucormycosis.

KOH positivity was seen in 62% of patients. Among the fungal culture mucorale were isolated in 59.3% and Rhizopus species were the commonest species identified consisting of 44.8% of total fungal culture while mixed fungal growth was seen in 3.9% growth and bacterial co-infection has been reported in 36.3% culture.[18]

The mainstay of antifungal therapy is amphotericin B. Pooled results showed that total amphotericin B has been given in 93% of COVID-19-associated ROCM patients among which liposomal amphotericin B has been given in 90% of patients. Other antifungals used in the management of ROCM patients were voriconazole. Other treatments are broad-spectrum antibiotics, tocilizumab, vasopressor, ionotropic agent, and IV dexamethasone. Prakash et al[19] conducted a study and concluded that mechanical debridement was done in 70.9% of ROCM patients.

The overall prognosis is poor with mortality ranging from 33.3% to 80%. Goel A et al[20] proposed that histopathologic features can be used as prognostic tool to help doctors choose the best surgery, chemotherapy, and immunosuppressive options at the time of tissue diagnosis. The microscopic features listed below were used:

• Fungal load (graded as mild, moderate and marked) and the respective survival rates were 75% 63% and 57%.

• FUNGAL ELEMENTS' MORPHOLOGY

The average diameter of five randomly selected hyphae in the area of maximal fungal load under high power objective was used to calculate the mean diameter of the fungus in each case (x400). A Leitz Wetzler ocular micrometre was used to measure the diameter.

•INFLAMMATORY INFILTRATE COMPOSITION
Depending on the severity of the infiltrate, they graded the presence of neutrophils and granulomatous reaction was rated (mild, moderate, and marked).

• THE EXTENT OF THE TISSUE NECROSIS

Tissue necrosis was measured as a percentage of the total area of the sampled tissue.

• FUNGUS INVASION OF TISSUE

The diameter of the fungus was also shown to be a significant (P = 0.04) finding in this series of histology factors. Patients with chronic rhino-orbito-cerebral zygomycosis had a considerably better prognosis (P = 0.01) than those with acute rhino-orbito-cerebral zygomycosis.

Chakrabarti A et al[21] 2020 described various novel therapeutic options for Mucormycosis management (Figure 6). They concluded that MANOGEPIX (MGX) is a novel antifungal agent and acted by targeting Gwt1 in the eukaryotic glycosylphosphatidylinositol (PGI) post-translational modification pathway of surface proteins. US (FDA) - oral and intravenous formulations (fosmanogepix) (APX001) -treatment of seven fungal infections including Mucormycosis. CALCINEURIN- too plays an important role by shifting the growth of Mucor to a less virulent yeast form.

Anand VK et al[22] described various complications of Mucormycosis such as:

- Cavernous Venous Sinus Thrombosis
- Orbital Apex syndrome
- Brain Abscess
- Garcin syndrome
- Internal Carotid Artery Occlusion
- Hemiparesis
- Hemiplegia
- Coma
- Death

Rapid AD et al[23] conducted a study on the prognosis of Mucormycosis and mortality rates were found to be 15–34%. The overall survival rate was found to be 50%.

Honavar SG[24] 2021 described various prevention options for Rhino-orbito-cerebral mucormycosis in the setting of COVID-19. These are as follows:

- Judicious and supervised use of systemic corticosteroids in compliance with the current preferred practice guidelines.
- Aggressive monitoring and control of diabetes mellitus.
- Strict aseptic precautions while administering oxygen (sterile water for the humidifier, daily change of the sterilized humidifier and the tubes).
- Personal and environmental hygiene.
- Betadine mouth gargle.
- A barrier mask covers the nose and mouth.
- Consider prophylactic oral Posaconazole in high-risk patients.

4. CONCLUSION

Patients with COVID-19 infection are susceptible to mucormycosis due to impaired barrier defense, phagocyte and lymphocyte dysfunction, and the use of immunosuppressive medicines such as steroids. In such individuals, treating clinicians must be mindful of the likelihood of mucormycosis, especially in those with underlying comorbidities. Early and prompt diagnosis and management of secondary fungal infections can reduce morbidity and mortality rates significantly.

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