POST COVID MANDIBULAR MUCORMYCOSIS: A CASE REPORT

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ABSTRACT

Mucormycosis is an opportunistic fungal infection associated with high mortality rate occurring in patients with impaired immunity and critically ill state. Early diagnosis and treatment can reduce mortality and morbidity of the patients. Here, we present a case of oral mucormycosis in a patient of COVID-19 infection. With this case, we highlight the unholy association of this mycotic infection with COVID-19 patients having diabetes.

Key Words : Mucormycosis, Covid, Aseptate hyphae, Sporangium.

INTRODUCTION:

Post COVID-19 sepsis is what occurs after SARS- CoV-2 and has marked rampage in the human body. It leads to a deranged innate immune response, thrombo-inflammation, cytokine storm, microvascular coagulation, ciliary dysfunction and eventual immune exhaustion. This cascade of events facilitates secondary bacterial and fungal infections especially in critically ill patients.[1] Mucormycosis is an opportunistic fungal infection associated with high mortality rate occurring in this kind of patients with immunocompromised and critically ill state.[2]

Mucormycosis, also known as zygomycosis or phycomycosis, a saprophytic fungus found in bread molds, soil and decaying fruits and vegetables.[3] These organisms belong to the order Mucorales of the subphylum Mucoromycotina and phylum Glomeromycota. Zygomycosis, as was originally described, included two clinicopathologically different diseases, mucormycosis and entomophthoromycosis.[4] They are ubiquitous with worldwide distribution and thermo-tolerant, growing on decaying organic matter.[2]

Oral cavity involvement usually appears as palatal ulceration or necrosis and occurs as a result of infection in the nasal cavity or paranasal sinuses. Patients often exhibit fever, nasal discharge, facial cellulitis and anesthesia, necrotic turbinates, headache, and lethargy. Occasionally the involvement of the buccal mucosa, maxillary alveolar ridges, upper lip, lower lip, and mandible is seen. In majority of cases, the disease has either pulmonary, gastrointestinal, or rhinocerebral manifestations.[3]

In microscopic sections, mucormycosis appears as broad (4 to 20 microm), non-septate hyphae that exhibit obtuse or right-angle branching.[3] The fungal hyphae can be seen in tissue sections stained with Periodic Acid-Schiff (PAS), Hematoxylin and Eosin and Methanamine Silver stains. The organisms can also be cultured on

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Sabouraud's glucose agar or identified by their characteristic carbohydrate assimilation patterns.[5]

Here, we present a case of oral mucormycosis in a patient of COVID-19 infection. With this case, we also highlight the unholy association of this mycotic infection with COVID-19 patients having diabetes.

CASE HISTORY:

Amidst the Covid 19 pandemic, a 63 years old male patient reported with a chief complaint of pain and non-healing lesion on left posterior alveolar region of mandible. He recalled noticing ulceration in the lower jaw and associated pain since past 2 weeks, which has increased since.

The patient presented with a previous history of hospitalization due to Covid 19 and had been negative since the last 25 days, as per RT-PCR reports. He was on steroid injections, antivirals and oxygen support for two weeks during his treatment. Patient also had history of Diabetes and Hypertension and was on medication for both for more than 20 years.

Owing to the patient's medical history and the rapid spread of the lesion, an in-depth clinical examination of the patient was performed. Intraoral examination revealed multiple missing teeth and moderate grade periodontal disease. The alveolar gingiva in place of missing left mandibular premolars and the attached gingiva buccal and lingual to the left mandibular first molar was brownish (Figure-1) in appearance; and demonstrated a well-delineated slough on the surface. The lesion was growing in size with pus discharge and pain, indicative of infection.

A panoramic radiograph was made, that revealed a prominent inherent bone loss associated with the mandibular left first and second molars (Figure-2). The palate, floor of the mouth, tongue, nasal mucosa and nasal septum were unremarkable.

Tout de suite, surgical extraction of mandibular first and second molar was done along with the removal of necrotic bone and gingivae. One brownish white soft tissue (measuring 1.0 cm. X 0.5 cm.), one large bony tissue (measuring 3.0 cm. X 0.8 cm.) and few small bony bits were removed; and the remaining bone and gingivae were thoroughly debrided, leaving only healthy tissue in the region (Figure-3).

Histopathological assessment of both soft and hard tissues was done. The H n E stained sections of soft tissue specimen revealed an inflamed infected connective tissue with perivascular and angioinvasive mucormycosis. The hyphae were wide, non-septate, occasionally branched at right angles, and look empty on haematoxylin and eosin. PAS section showed magenta stained hyphae. Typical terminal sporangium was also notable (Figure-4). Numerous clusters of bacterial colonies were seen along with surface fibrinous exudate (Figure-5). Many mixed inflammatory cells were noticeable with abundant acute cell component too. The decalcified H n E stained sections of bone revealed bony trabeculae affected with bacterial clusters and many mucormycotic hyphae in the marrow spaces (Figure-6). Empty osteocytic lacunae with many resting and reversal lines were seen. Moderate inflammatory response was also

noticeable. All these findings were suggestive of Mucormycosis associated with Bacterial superinfection.

After the final diagnosis was made, the patient was placed on antifungal therapy of Amphotericin B. proper hygiene and regular follow up was advised. The patient is currently stable and prosthetic rehabilitation shall be duly planned.

DISCUSSION:

While we struggle with COVID-19, the issue of post COVID-19 mucormycosis has emerged as a major problem.[1] In healthy individuals, there are various defense mechanisms which act against these opportunistic infections from cropping up, like the intact skin/mucosal barrier prevent infection even if spores come in contact;[6] mononuclear cells provide host defense; tissue macrophages phagocytose the spores and kill; neutrophils produce pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α), interferon-gamma (INF-γ), interleukin-1b (IL-1b), which in turn activate and recruit other inflammatory cells;[7,8] platelets secrete granules that have pro-inflammatory and anti-inflammatory cytokines and chemokines with fungicidal properties;[9] and natural killer (NK) cells exert direct and indirect cytotoxic effects and damage the hyphae of Mucorales.[10]

The use of corticosteroid treatment and anti-IL-6-directed strategies in COVID 19 patients, makes them highly defenseless hosts along with high fungal spore counts in the environment creates the full-fledged setting for mould infections.[1] Heavy mould spore counts even in hospital air have been found in various studies from hospitals across the country, due to predominantly hot, humid conditions in our tropical climate.[11] Hyperglycemia with ketoacidosis also increases the risk for mucormycosis. Changes in iron availability to the fungus may play a significant role in the pathogenesis of mucormycosis in these patients.[7,12]

Rhizopus oryzae has been found to be the most frequent etiologic agent of mucormycosis. The genome sequencing of Rhizopus oryzae has revealed that in its evolution, the organism has acquired the proficiencies for maintaining growth and metabolism under highly diversified environmental conditions, by the production of virulence factors, capacity for accelerated fungal cell wall synthesis, and iron assimilation[12,13]. The organism can evade and survive against host immunity and hostile environment, shows rapid angio-invasive growth, derive nutrition from the host and develop resistance to antifungal agents because of these genetic adaptations.[14]

Mucorales express spore coat homologue (CotH) proteins that help in adhering to the glucose-regulator protein 78 (GRP78) on the endothelial cells.[2,15] Endocytosis of fungus occurs by this interaction result in endothelial damage. Platelet-derived growth factor receptor (PDGFR) promotes endocytosis. PDGF regulates cell growth and division, particularly angioinvasion.

Upon invading the host, Mucorales derive nutrients from the host and escape the immune mechanism and start disseminating.[2]

Hyperglycemia with ketoacidosis in uncontrolled DM causes glycosylation of iron sequestering proteins transferrin, ferritin, and lactoferrin, reducing their iron

affinity and the presence of ketone bodies like β-hydroxy butyrate [BHB] and the low pH in the blood vessels strongly impairs the ability of transferrin to chelate iron, resulting in increased free iron levels. Glucose, iron, and BHB induce the expression of GRP78 and CotH, all result in the growth of the fungus and augmented fungal invasion, followed by injury of the endothelium. T-lymphocyte induction, IFN-γ production, and phagocyte-mediated killing is markedly suppressed.[2]

Because of angioinvasive nature, Mucorales use hemoglobin as source of iron.[2]

Bacteria/ fungi secrete an iron chelator called siderophores that bind iron with an affinity that surpasses that of transferrin and lactoferrin.[6] But the intrinsic siderophore, rhizoferrin secreted by Rhizopus, is inefficient in obtaining iron from the serum.[2] So, mucorales are dependent on free iron in the serum and readily use in diabetic ketoacidosis and of iron reductases or hemeoxygenases for rapid iron uptake.[14]

Calcineurin is a fungal virulence factor which has a central role in various fungal physiologic processes, including pathways that counteract the detrimental effects of antifungals and promote resistance. The antifungal resistance is also said to be carried by Mendelian mutations or epigenetic pathways.[2]

Involvement of the oral cavity usually appears as palatal ulceration or necrosis and occurs as a result of infection in the nasal cavity or paranasal sinuses.[3] Patients often exhibit fever, headache, facial cellulitis and anesthesia, nasal discharge, necrotic turbinates, and lethargy. Occasionally the involvement of the buccal mucosa, maxillary alveolar ridges, upper lip, lower lip, and mandible is seen.[3] In majority of cases, the disease has either pulmonary, gastrointestinal, or rhinocerebral manifestations.[3] The most important manifestations of Mucormycosis in cases of COVID 19 are rhino-orbital-cerebral and pulmonary.[1] If left untreated the diseases may spread into the brain resulting in death.[3]

Histopathologic examination of the hard tissue specimen reveals necrotic compact and cancellous bone trabeculae that may exhibit irregular surface resorption. Masses of organisms may be found within the bone marrow spaces and resorptive crypts. Some of these are elongated, broad, non-septate branching hyphae that contained terminal globose sporangia & clusters of spores. The soft tissue specimen demonstrates mucosa, submucosal tissue and attached bone fragments that contained a dense infiltrate of lymphocytes, plasma cells and polymorphonuclear leukocytes.[3]

Treatment principles include antifungal drugs, surgical debridement, removal of underlying predisposing factors and adjuvant therapy. Amphotericin B has been the standard of treatment for invasive mucormycosis.[1]

CONCLUSION

The current case brings to light the apparent rapid and invasive spread in Mucormycosis leading to morbidity. Timely diagnosis and proper treatment planning goes a long way in preventing mortality, the importance of which needs to be underscored.

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FIGURES:

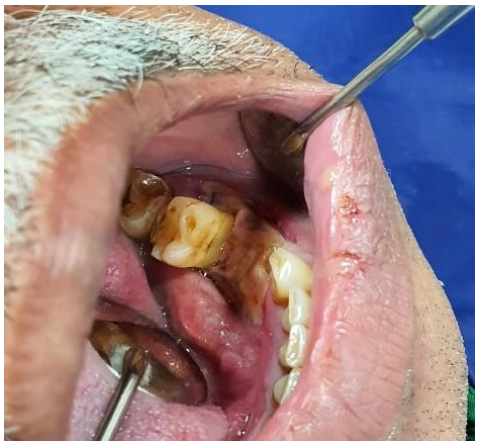

FIGURE 1: Intraoral view depicting greyish brown colored slough and debris in the posterior left mandibular area.

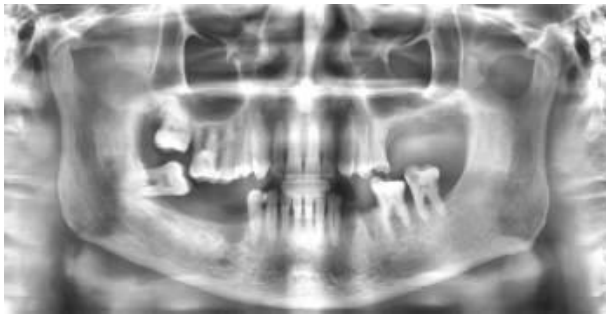

FIGURE 2: Pre-op OPG revealing multiple missing teeth and horizontal bone loss in the posterior regions of jaw. 36, 37 region associated with the clinical lesion area represents inter-radicular defect.

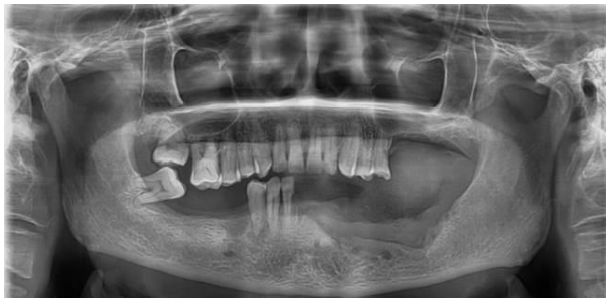

FIGURE 3: Post-op OPG revealing surgical bony debridement along with extraction of 36 and 37.

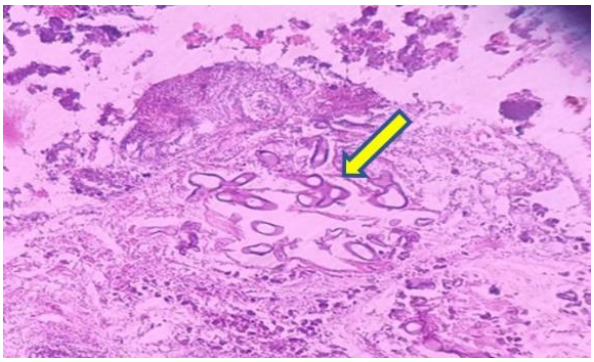

FIGURE 4: Photomicrograph of soft tissue specimen revealing numerous aseptate empty appearing fungal hyphae with occasional perpendicular hyphal branching and sporangia (Haematoxylin and Eosin stain; Magnification X 400).

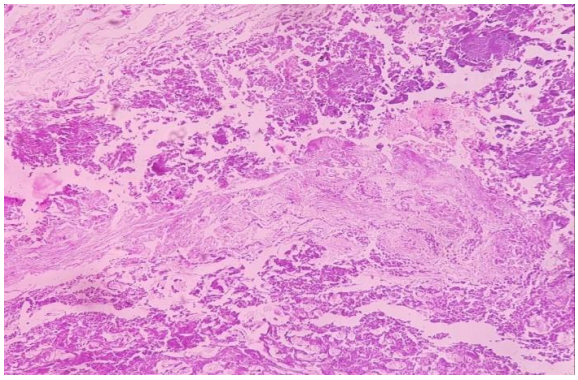

FIGURE 5: Photomicrograph of soft tissue specimen showing many clusters of bacterial colonies suggesting superinfection (Haematoxylin and Eosin stain; Magnification X 100).

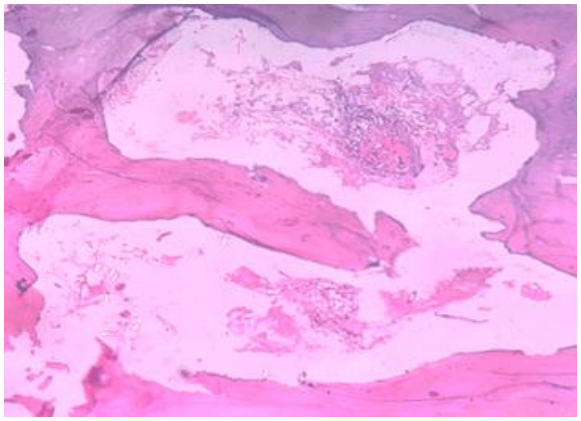

FIGURE 6: Photomicrograph of decalcified bony specimen showing many bony trabeculae with apparently empty appearing lacunae and many clusters of fungal hyphae along with bacterial colonies in the intervening marrow space (Haematoxylin and Eosin stain; Magnification X 100).