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Post Covid-19 Mucormycosis: A Sudden rising trend

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Abstract

Introduction: Mucormycosis appears as the diabetes-defining illness and remains one of the complications in uncontrolled diabetic patients with mortality rates ranging between 40-80%. India contributes to 40% of the global burden of this "rare mould" infection as it is called in western literature, with an estimated prevalence of 140 cases per million population.

We have found very few articles reporting on fungal co-infections in patients with history of covid-19. We report a series of cases which presented to us and their effective management and a review of it.

Discussion: The current rise in incidence of cases of mucormycosis has set an unprecedented alarm. Mild to moderate cases of covid 19 infections, followed by newly diagnosed cases of diabetes mellitus has set a route for opportunistic fungal infections. COVID-19 is associated with a significant incidence of secondary infections, both bacterial as well as fungal probably due to immune dysregulation. Mucormycosis in maxilla is very rare and because of its nonspecific symptoms, diagnosis is very challenging. Treatment principles broadly include antifungal agents, surgical debridement, reversal of underlying predisposing factors and adjuvant therapy. Amphotericin B has been the standard of treatment for invasive mucormycosis.

Conclusion: Mucormycosis developing in the post COVID-19 setting 'breaks the back' of a patient's family that is barely recovering from a deceptive viral infection. This scenario is nothing but the short of 'Recovery from the frying pan and into the fire.'

Keywords: Mucormycosis, Covid 19, Diabetes Mellitus, Fungal Infection.

Introduction

While our country battles with COVID-19, the issue of post COVID-19 sepsis has emerged as a significant problem. India bears the dubious distinction of being both the diabetes and the mucormycosis. The 'capital' of the

world. COVID-19 and its treatment, against this backdrop, amounts to a recipe for disaster.[1]

Mucormycosis is a fungal infection which is comparatively rare in in the maxillofacial region. Fungal species such as rhizopus, rhizomucor and mucor are responsible for development of mucormycosis.[9] Rhizopus oryzae is the most common organism responsible for 70% of all cases of mucormycosis. The major risk factors for mucormycosis include uncontrolled diabetes mellitus with ketoacidosis, elevated serum iron levels, other forms of metabolic acidosis, treatment with corticosteroids, neutropenia, trauma and burns, malignant hematologic disorders, and deferoxamine therapy in patients who are receiving haemodialysis.[2]

With an estimated 77 million cases in the adult population, diabetes is India's fastest growing epidemic. The unholy association between diabetes and the severity of SARS-CoV-2 infection has been established in various studies across the world.

Mucormycosis appears as the diabetes-defining illness and remains one of the complications in uncontrolled diabetic patients with mortality rates ranging between 40-80%. India contributes to 40% of the global burden of this "rare mould" infection as it is called in western literature, with an estimated prevalence of 140 cases per million population.[1]

We have found very few articles reporting on fungal co-infections in patients with history of covid-19. We report a series of cases which presented to us and their effective management and a review of it.

Case Reports

A 55 year old male patient reported to us in the month of August with complain of pain over face and signs and symptoms which were suggestive of maxillary sinusitis. Patient had already undergone nasal endoscopic drainage of sinusitis 2 weeks back, during which the content was sent for histopathologic examination, which confirmed the diagnosis of Mucormycosis. Patient had history of covid-19 infection 1 month back and sudden onset of diabetes post covid infection. At the time of presentation, patient was also started on Antifungal Inj. Amphotericin-B and was treated with surgical debridement of entire right maxillary sinus. A total stay of 14 days consisting of antifungal therapy and effective management of uncontrolled diabetes, was effective in complete treatment of the disease. An 8 month follow up of the patient has been kept to check for any recurrence.

A second case was of 66 year old female who had recently recovered from Covid-19 and already had systemic diseases like Diabetes Mellitus and Hypertension as well as rheumatoid arthritis. Patient complained of multiple draining sinuses from the entire maxillary arch (Refer Fig. 1) and on incisional biopsy, it was confirmed as Mucormycosis. CT PNS was done (Refer Fig. 1) to check the extent of the lesion, indication of entire maxillary arch being involved with complete involvement of the right maxillary sinus. Similar line of treatment was followed, control of the systemic diseases along with antifungal therapy using Inj. Liposomal Amphotericin-B 50 mg twice a day for 14 days, regular renal function tests were done to keep a check on serum creatinine levels, for any sign of nephrotoxicity. Complete debridement of the maxilla was done. (Refer Fig. 1)

A third and fourth case was of 40 year old females, with a similar history of Covid-19 infection 2 months back and history of multiple extractions in upper arch, patient complained of multiple draining sinuses as well non healing sockets in the upper arch. Histopathologic examination of the exposed necrosed bone and the maxillary sinus lining revealed presence of non-parallel fungal hyphae suggestive of Mucormycosis. CT PNS was done and a similar line of treatment was advocated.

A case of Rhino-orbital Mucormycosis, 38 year old patient reported with a complaint of swelling over right side face and proptosis and vision loss with respect to right eye, high grade fever, raised blood sugar levels, past medical history of Covid-19 infection 20 days back and multiple draining sinuses over the buccal mucosa bilaterally. CT PNS showed pansinusitis, with overlying soft tissue inflammatory changes and bony defects over right maxilla, zygomatic buttress and anterior wall of maxilla. Bony defect over medial wall of right orbit, bulky soft tissue causing lateral displacement resulting into mild proptosis. (Refer Fig. 2)

Aggressive surgical debridement of bilateral maxillary and ethmoidal sinuses along with orbital exenteration of right eye was done under GA. Patient was kept on anti-fungal therapy for a period of 21 days using Inj. Liposomal Amphotericin B. (Refer Fig. 3)

Increased Serum Iron ferritin levels were reported for all patients.

Discussion

The current rise in incidence of cases of mucormycosis has set an unprecedented alarm. Mild to moderate cases of covid 19 infections, followed by newly diagnosed cases of diabetes mellitus has set a route for opportunistic fungal infections. There have been a considerable rise in the number of cases of Mucormycosis, with an incidence of only 4-5 cases in last 3 years to 6 cases in last 6 months reporting to our institution. There are chances that the immunosuppressive treatment used for COVID-19 is making the patients more susceptible to mucormycosis.

COVID-19 patients with trauma, diabetes mellitus, and prolonged neutropenia are more likely to develop mucormycosis. To confirm the diagnosis, non-pigmented hyphae showing tissue invasion should be shown in tissue sections stained with hematoxylin–eosin (HE), PAS or GMS. Culture of specimens is strongly recommended for identification of genus and species.

The treatment recommendations can be supported by the global guideline for the diagnosis and management of mucormycosis in 2019 by European Confederation of Medical Mycology (ECMM) and Mycoses Study Group Education and Research Consortium that the therapeutic and alternative medication used for mucormycosis have been given more opinions. Generally, it strongly supports an early complete surgical treatment for mucormycosis whenever possible, in addition to systemic antifungal treatment. [3]

While COVID-19-associated pulmonary aspergillosis (CAPA) has received much international attention, the Indian epidemiology of invasive mould infections in the ICU reveals a significant burden of invasive mucormycosis. This has been recently reported as a life threatening complication of COVID-19 in our country. Although the predisposing factors and pathogenesis are somewhat similar to that of other mould infections, certain unique characteristics and key distinguishing factors are there in order to promptly suspect the infection, confirm the diagnosis and offer therapeutic intervention. [1]

Unlike CAPA, invasive mucormycosis has been observed even in patients with mild to moderate SARS- CoV-2 infections. The strongest predisposing factor appears to be hyperglycaemia in undiagnosed or uncontrolled diabetics. Hyperglycaemia leads to increased expression of the endothelial receptor GRP78, resulting in polymorphonuclear dysfunction, impaired chemotaxis and defective intracellular killing. An important virulence trait of Mucorales is the ability to acquire iron from the host which is an essential element for its growth. In conditions of ketoacidosis, free iron readily available in the serum. This excess endogenous iron is efficiently taken up by the Mucorales through siderophores or iron permeases, further

leads to enhancement of their virulence. These effects are greatly amplified by the use of corticosteroids and immunosuppressant's in susceptible hosts. Corticosteroids themselves cause impairment in the neutrophils migration, ingestion, and phagolysosome fusion. Coupled with the potential implications of steroid-induced hyperglycaemia, the diabetic COVID 19 patient receiving corticosteroids or other immunosuppressant's is exceptionally more vulnerable to the development of mucormycosis.[1] However, there are some cases of Covid-19 who have received no treatment with steroids were also seen to be infected with this fungal infections. Use of corticosteroids in patients with covid 19 and uncontrolled diabetes can be one of the pre-disposing factors for fungal infections.

Fungal hyphae produce "rhizoferrin", which binds to serum iron. The rhizoferrin iron complex is important for fungal growth.[4,5] Hence, patients with diabetic ketoacidosis are more susceptible to mucormycosis as they have elevated levels of serum iron. Increased serum ferritin levels as a result of COVID-19 related hyper-inflammation signify a vicious cycle of events where increased ferritin levels may lead to further tissue damage.[6] This increases the chances of patients suffering through fungal infections.

One of the reasons why there are such a high number of cases of uncontrolled diabetes mellitus is also due to the lack of follow ups taken during the lockdown period, of patients suffering from diabetes. Being highly influenced by a particular lifestyle, eating habits, lack of exercise during the lockdown period, a lot of patients suffering from diabetes were not able to keep a check on their blood sugar levels. Also during the lockdown period, patients were unable to visit dentists for follow ups leading to persistence of long standing infection for months.

COVID-19 is associated with a significant incidence of secondary infections, both bacterial as well as fungal probably due to immune dysregulation. The two most important manifestations of Mucormycosis are rhino-orbital-cerebral and pulmonary. Suspicion is based on subtle clinical and imaging clues, risk factors and disease development or progression while on any antibacterial or antifungal therapy that does not cover Mucor.[1,7]

The clinical hallmark is tissue necrosis manifested as a necrotic lesion, eschar or black discharge in the nasal or oral cavity. Orbital, ocular and cranial nerve involvement are menacing signs. Alternative erroneous diagnoses lead to antibacterial and further steroid use which add fuel to the fire. There are no specific biomarker for the diagnosis of mucormycosis and hence a negative galactomannan and beta-d-glucan are useful pointers to rule out other mould infections.

Rapid diagnostic methods include biopsy, KOH mount and Calcofluor stain. Mucor is difficult to routinely culture. Biopsy remains the central component for diagnosis and the benefits of the procedure outweigh the risk, even in a 'difficult to access' location or in the presence of coagulopathy. The site of biopsy must be taken into consideration in this cases, maxillary sinus lining is the first involved site and should always be sent for histopathologic examination in suspected cases of mucormycosis.[1]

Mucormycosis in maxilla is very rare and because of its nonspecific symptoms, diagnosis is very challenging. Maxilla being highly vascularized compared to mandible, it seems obvious as to why mandible would be more commonly affected as seen in cases of bacterial infections like osteomyelitis. The collateral blood supply, porous nature of bone, and thin cortices of the maxilla reduce the chance of infections in the maxilla as compared to the mandible. However, our series showed a predominance of mucormycosis in the maxilla over the mandible. One of the reasons being the presence of maxillary sinus which

acts as a hub for different bacterial colonization. Mucormycosis is an opportunistic fungal infection, in which the fungus invades the arteries, leading to thrombosis that consequently leads to necrosis of the hard and soft tissues. Fungal infections of the facial bones needs to be investigated thoroughly as there is no difference in clinical presentation between bacterial and fungal infections unless it is accompanied by maxillary sinusitis. The diagnostic workup with biopsy and culture sensitivity helps to identify the pathogen at the earliest.[4]

The management of mucormycosis is based on multiple intermediations occurring simultaneously. The basic principles of mucormycosis treatment include severity of the diseases, and intense efforts for early, clinical and laboratory diagnosis; timely introduction of an operational antifungal therapy along with aggressive surgical debridement of necrotic lesions; and when feasible control of the underlying medical condition. Early diagnosis and prompt therapeutic intermediation may prevent advanced tissue invasion and its sequelae, may also reduce the need for extensive surgery and ensuing deformity, and may improve survival. [8]

Treatment principles broadly include antifungal agents, surgical debridement, reversal of underlying predisposing factors and adjuvant therapy. Amphotericin B has been the standard of treatment for invasive mucormycosis. COVID-19 patients may develop an acute or chronic renal failure which may be managed by switching to a less- or non-nephrotoxic alternative. In such a condition, Inj. Liposomal Amphotericin B, posaconazole or Isavuconazole can be used. Surgical debridement, the earlier the better, is pivotal in the management of mucormycosis.

Surgical resection of necrotic tissue is the mainstay of mucormycosis therapy.[8] Therapy is toxic and very resource intensive. In a recent Indian study, 24.3% patients left the hospital against medical advice due to the anticipated cost, morbidity of surgery and prognosis.

Mucormycosis developing in the post COVID-19 setting 'breaks the back' of a patient's family that is barely recovering from a deceptive viral infection. This scenario is more like 'Recovery from the frying pan and into the fire.'[1]

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Legend Figures

Figure 1 A: Pre-operative photograph

Figure 1 B: Pre-Operative CT PNS

Figure 1 D: Intra-Operative Photograph: Debridement of Maxilla done

Figure 1 C: Post-Operative Photograph

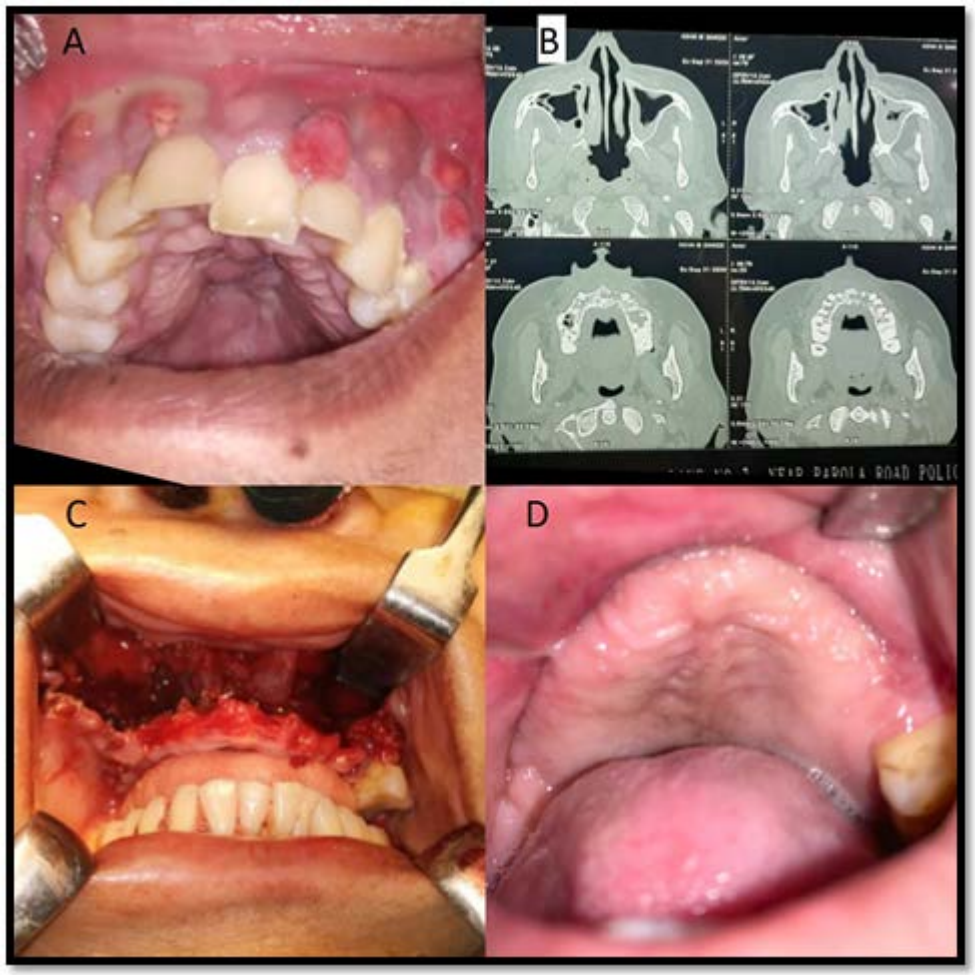

Figure 2: CT PNS

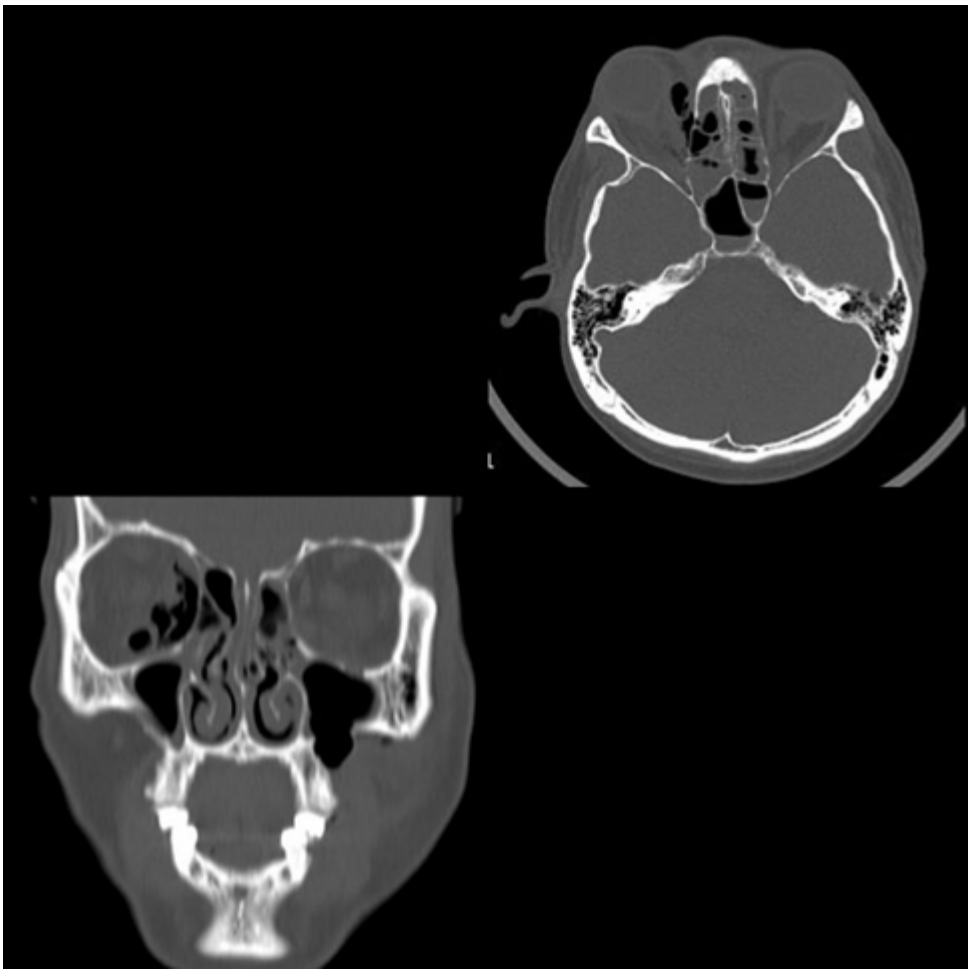

Figure 3: Orbital Exenteration