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A Special Case Report of Mucormycosis with Insight into its Pathophysiology

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Abstract: ***Mucormycosis is a deadly opportunistic disease caused by a group of fungi named mucormycetes. Several case series and studies have been documented since the pandemic coronavirus disease 2019 (COVID-19), suggesting the possibility of COVID-19associated mucormycosis. But there have only been a very small number of reportsonmucormycosis in patients with mild COVID-19 infection or without COVID-19 infection. This is a case of rhinomaxillary mucormycosis in a 42-year-old man with diabetes mellitus, leptospirosis and mild COVID-19 infection.***

Keywords: COVID 19, Diabetes mellitus, Leptospirosis, Mucormycosis, Mucorales

1. Introduction

Mucormycosis (phycomycosis, zygomycosis) is a rare opportunistic fungal infection caused by the fungus Mucor, which is a member of the Mucoraceae family and the Mucorales order. The word "mycosis mucorina," originally coined by Paultauf in 1885, was first used to describe it.[1] It ranks third among angioinvasive fungal infections after aspergillosis and candidiasis. It usually affects the immunocompromised individuals and is rarely seen in apparently healthy individuals. Mucormycosis infection in the compromised host occurs from impaired immunity, which leads to the fast proliferation and invasion of fungal organisms in deeper tissues. Numerous risk factors, including poorly controlled diabetes mellitus, end-stage renal disease, neutropenia, immunosuppression or chemotherapy, rheumatic or autoimmune disorders, peritoneal dialysis, iron overload states, malnutrition, trauma, and burns, have been linked to the progression of mucormycosis.[2]However, in some cases of mucormycosis, individuals have no observable risk factors. Inhalation of spores through the mouth, nose, or even a skin laceration is the transmission route of pathophysiology. In individuals with impaired defense mechanisms, the fungus may then spread to the paranasal sinuses, orbit, meninges and brain by direct extension which is fatal.[3]We present here a case of maxillary mucormycosis in a diabetic patient with prior leptospirosis and COVID-19 infection.

2. Case Report

A 42-yearold male patient presented to the out-patient department with a chief complaint of pain and mobility in the upper left back teeth region. He had chronic intermittent pain since past one year and had taken painkillers, but the pain didn't subside. He was reluctant to visit the dentist and reported it after one year when he noticed mobility in the upper back teeth and occasional bleeding while brushing teeth. He had nasal regurgitation during fluid intake. The patient was a chronic alcoholic, a smoker and a betel quid chewer since 20 years of age. He had quit these deleterious habits 2 years ago. His medical history revealed that he had type 2 diabetes mellitus for six years and was on treatment with oral hypoglycemic drugs**.**

Two years ago, the patient had a COVID-19 infection. Mild symptoms such as temperature, headache and malaise afflicted him. He received supportive treatment while being under home quarantine. He was not immunized against COVID-19. His kidney function diminished after 6 months as a result of leptospirosis infection, and oral hypoglycemics were then discontinued. This led to uncontrolled diabetes mellitus and he was advised to start insulin administration. He started experiencing pain in his left upper back teeth after a few months.

On extraoral examination, there was no swelling or facial asymmetry. On palpation, the left maxillary sinus area was tender. The lymph nodes could not be palpable. Denuded mucosa with exposed necrotic gray-colored bone that extended buccally and palatally involving the alveolar ridge in the vicinity of teeth 24to 28 was noticed during intraoral examination (Figure 1). The mucosa in the area was sloughing and seemed brownish. Halitosis was present. The teeth had stains and calculus. The affected area was rough in texture and tender on palpation. Grade 3 mobility of teeth 24 to 28 with exposure of their roots were noted along with segmental mobility of the corresponding dentoalveolar segment. A deep fungal infection affecting the maxilla was tentatively diagnosed based on the patient's medical history and clinical symptoms, with osteomyelitis, necrotising periodontitis and chronic granulomatous infection being potential differential diagnoses.

A paranasal sinus view (PNS) radiograph revealed haziness of the left maxillary sinus with destruction of the sinus walls, whereas an orthopantomogram revealed no significant

changes. A computed tomography (CT) scan revealed areas of erosion and fragmentation in the left hemimaxilla with associated enhancing soft tissue in the left gingivobuccal sulcus. Superiorly, the lesion is eroding the floor of the left maxillary sinus and left posterolateral wall with extension into the maxillary sinus, suggesting chronic fungal infection (Figure 2). Bilateral maxillary, ethmoidal and frontal sinusitis were also seen. A nasal swab was taken and sent for fungal culture, but it was negative. An elevated fasting blood sugar level and decreased haemoglobin level were discovered during biochemical testing and the HbA1c level was 9%. Furthermore, cytological smears were taken from the alveolar and palatal regions and Papanicolaou staining revealed numerous aseptate fungal hyphae among epithelial and mixed inflammatory cells.

An alveolar incisional biopsy was performed, and microscopic examination of decalcified sections under H&E revealed necrotic bone interspersed with fungal hyphae. These fungal hyphae were broad and aseptate, with branching at right or obtuse angles (Figure 3). Round to ovoid sporangia were also noted. There were also hemorrhagic areas and a chronic inflammatory cell infiltrate. On staining the sections with Periodic acid–Schiff-stain, magenta -coloured aseptate fungal hyphae with branching at right angles were seen (Figure 4).GMS staining was used to reveal numerous black-colored fungal hyphae that are nonseptate and branch at 90° (Figure5). A final diagnosis of maxillary mucormycosis was made based on radiological and histopathological findings. For further treatment, the patient was referred to nearby tertiary health care centre where he underwentinferior partial maxillectomy and functional endoscopic sinus surgery (FESS) for maxillary sinus along with administration of Amphotericin B 10mg/Kg for 28 days.

3. Discussion

Mucormycosis incorporates a range of infections caused by Zygomycetes, a class of fungi that produce branching ribbon-like hyphae and reproduce sexually by formation of zygospores. The most pathogenic species of the family, Mucoraceae is Rhizopus. Rhizopus oryzae is the predominant pathogen which accounts for 60% of all the forms and 90% of the rhinocerebral cases.[4] Mucormycosis of the oral cavity can be of two different origins. One is from disseminated infection where the gateway of entry is inhalation (through the nose) and the other is through direct wound contamination with dissemination to other viscera as a common complication. A significant difference between infection involving the maxilla and mandible is cavernous sinus thrombosis, a serious complication of maxillary infections.[5]

Mucorales have many traits such as thermotolerance, rapid growth and angioinvasive nature, cell wall remodeling to endure hostile environments, iron uptake from the host, ability to bind to glucose-regulated proteins on endothelial cells, downregulation of host genes involved in the immune response and tissue repair, and resistance to most available antifungals. The fungus might enter the host through different routes, including spore inhalation, skin inoculation, or ingestion through the gastrointestinal tract. Independently of the inoculation route, the establishment of the infection depends on several steps: inoculation of spores, immune response evasion, attachment to the endothelium, endocytosis, germination into hyphae, endothelial damage, and hematogenous dissemination.[6] Thus far, the most studied Mucorales virulence factors that participate in the infection process are the attachment to endothelial cells and iron uptake. As Mucorales are vasotropic, the interaction between the fungus and endothelial cells around blood vessels is an indispensable step in mucormycosis pathogenesis, which explains the angioinvasive nature of these organisms.[7]

In India, mucormycosis was seen in 0.14 per 1000 population, which was 80 times higher as compared to developed countries.[8]In Asia, the most common risk factor for mucormycosis is diabetes mellitus (DM), while in North America and Europe, Hemetologic malignancies and organ transplants are far more popular. [9] Diabetic patients are predisposed to mucormycosis because of the decreased ability of their neutrophils to phagocytose and adhere to the endothelial walls. Furthermore, the acidosis and hyperglycaemia disrupt the ability of transferrin to bind iron, and this alteration eliminates significant host defense mechanism providingan excellent environment for the fungus to grow. Also in the diabetic ketoacidosis patient, there is an increased risk of mucormycosis caused by Rhizopus oryzae as these organisms produce the enzyme ketoreductase, which allows them to utilize the patient's ketone bodies.[10]Chakrabarti et al., who analyzed 178 cases of Zygomycosis in hospitalized patients in northern India, found co-existing, uncontrolled diabetes in 73.6% of the patients. Moreover, Schwartz et al., noticed that Cerebro-Rhino-Orbital Phycomycosis (CROP) which was mainly caused by Rhizopus species, occurred predominantly in the individuals with diabetic ketoacidosis.[4]

Frequent clinical presentations include rhinocerebral, pulmonary, and cutaneous forms (superficial) and less frequently, gastrointestinal, disseminated, and miscellaneous forms. The rhinocerebral (rhinomaxillary) form is the most common form of infection commonly seen in patients with uncontrolled diabetes mellitus.[11]Patients with rhinocerebral mucormycosis clinically present with malaise, headache, facial pain, and swelling and with low-grade fever. Differential diagnosis of lesion should include osteomyelitis, chronic granulomatous infection such as tuberculosis, tertiary syphilis, midline lethal granuloma, and other deep fungal infections. Radiographically, opacification of sinuses may be noticed in conjunction with patchy effacement of bony walls of sinuses. CT with contrast or magnetic resonance image scan can demonstrate erosion or destruction of bone and helps to know the extent of disease. Histopathologically, the lesion demonstrates broad aseptate fungal hyphae that show branching at right angles or obtuse angles.[12] In the present case, the same histopathology was revealed. The histopathological differential diagnosis includes aspergillosis where the hyphae of Aspergillus species are septate, smaller in width and branch at more acute angles.[13]When diagnosed early, mucormycosis may be cured by a combination of surgical debridement of the infected area and systemic administration of antifungals. Proper management of the underlying condition is also an

essential aspect affecting the prognosis ofthis fatal fungal infection.[14]

4. Conclusion

The prevalence of Mucorales in the community and hospital environment, the enormous number of susceptible hosts, particularly diabetics and the Indian population's neglect for regular health check-ups are all plausible reasons for the high prevalence. Many people are unaware of their diabetic status until they develop mucormycosis. Due to the delay in seeking medical assistance and diagnosing the condition, as well as difficulty in controlling the advanced stage of infection, the mortality rate linked with mucormycosis is rather high.[15]Hence early diagnosis and timely management are necessary to improve the outcome in cases ofmucormycosis.

5. Future Scope

More recently, mesenchymal stem cells (MSCs) have been used to exhibit immunomodulatory function and proven to be beneficial in a clinical cell-based regenerative approach. MSC-based therapy in mucormycosis along with the combination of short-term antifungal drugs can be utilized as a prospective approach for mucormycosis treatment with promising outcomes.[16] Large-scale studies need to be conducted to identify early biomarkers and optimization of diagnostic methods has to be established per population and geographical variation. This will not only help clinicians around the world to detect the infection in time but also will prepare them for future outbreaks of other potential pandemics.[17]

Declaration of patient consent: Patient consent was obtained.

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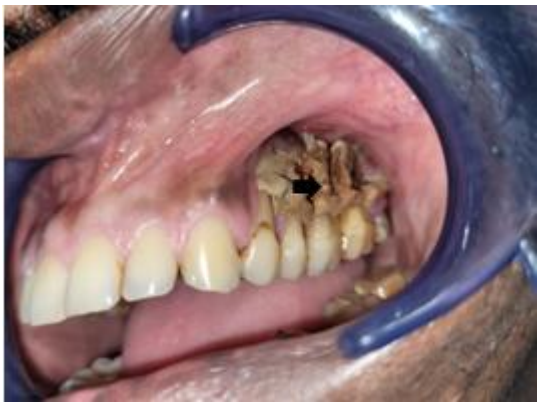

Figure 1: Areas of necrotic bone over left maxillary buccal aspect extending from 24 to 28 region with root exposure (black arrow)

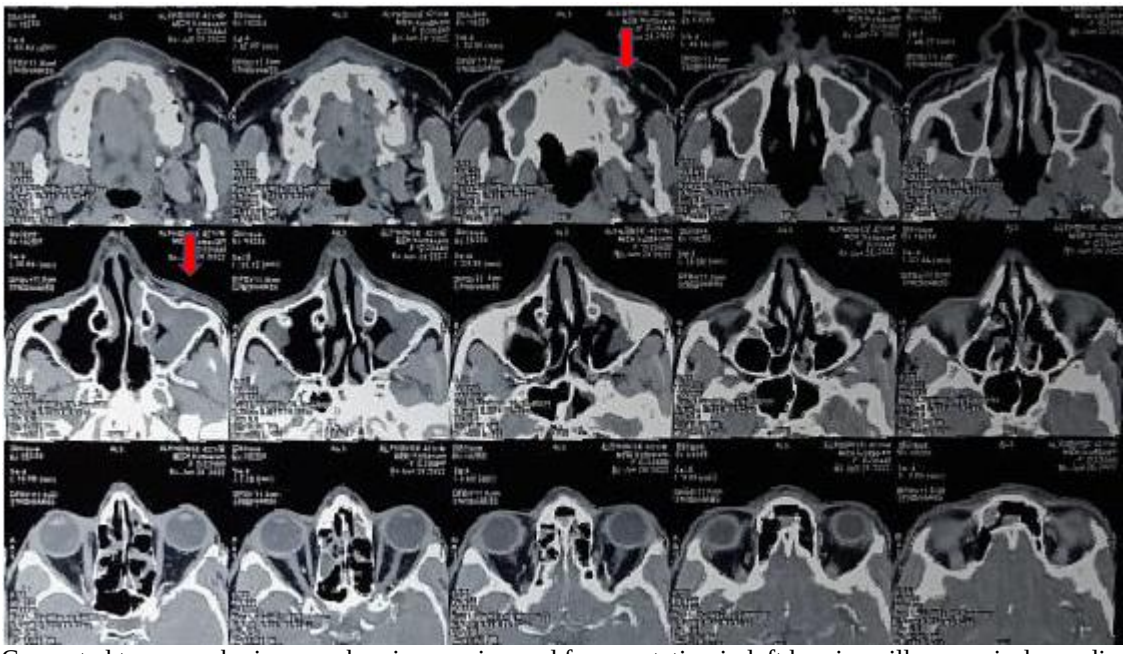

Figure 2: Computed tomography images showing erosion and fragmentation in left hemimaxilla, superiorly eroding the floor of left maxillary sinus and left posterolateral wall with extensions into maxillary sinus

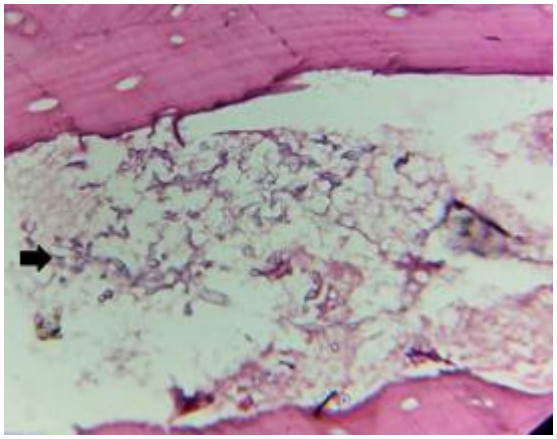

Figure 3: H and E-stained tissue section showing necrotic bone and aseptate fungal hyphae branching at right angles (black arrow)

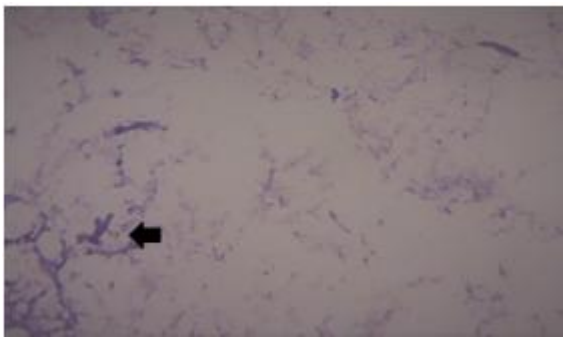

Figure 4: Periodic acid–Schiff-stained section showing magenta -coloured aseptate fungal hyphae (black arrow)

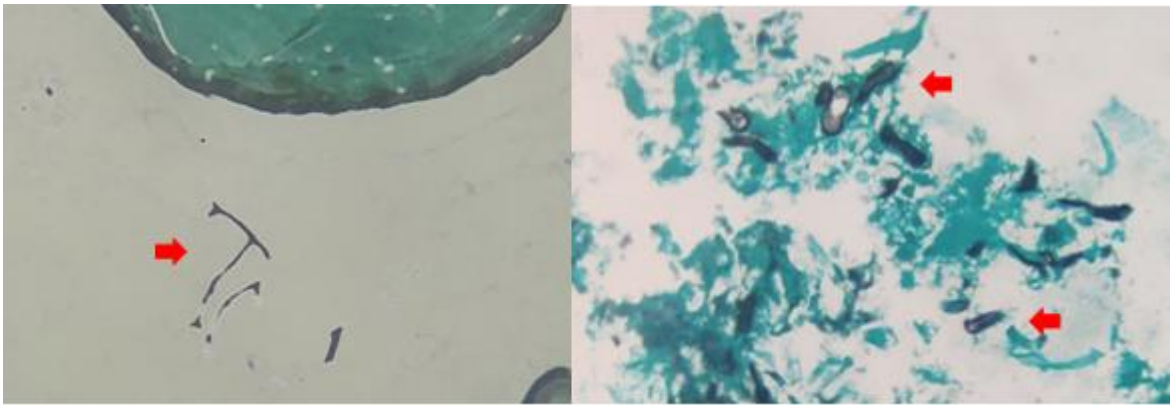

Figure 5: GMS stain showing colonies of black stained aseptate, fiamentous hyphae, some showing branching at 90 degree (red arrows)

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