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Triad of COVID-19, Diabetes mellitus and Mucormycosis: A mere coincidence or a Real Association ?

Arthi Srinivasan*

Department of Department of Microbiology, Saveetha Dental College and Hospitals,india

***Corresponding author:** Arthi Srinivasan, Department of Department of Microbiology, Saveetha Dental College and Hospitals,india, Tel: 9944455772; E-mail: amazonarthi@gmail.com

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ABSTRACT

Background

COVID-19 patients, especially severely ill or immunocompromised, have a higher probability of suffering from invasive mycoses. As a life-threatening infectious disease, COVID-19 patients showed overexpression of inflammatory cytokines, and impaired cell-mediated immune response with decreased CD4 + T and CD8 + T cell counts, indicating its susceptibility to fungal co-infection. Early diagnosis of mucormycosis is of utmost importance as studies have shown that it increases survival and it may also reduce the need for or extent of surgical resection and suffering. The chances for recovery from mucormycosis are low, despite early diagnosis and intensive combination surgical and medical therapy and the mortality of mucormycosis remains high.

AIM

The aim of the study is to analyse the clinical features and the severity of mucormycosis in post COVID-19 patients

Materials and Methods

A total of 12 patients were included in this study and all were tested positive for COVID and hospitalized. The data recorded were demographic variables, clinical features including the underlying systemic complications and COVID status, treatment done and the follow up of patients.

Results

All cases were histopathologically / cytologically reported as mucormycosis. The age of occurrence was in the range of 30 - 60 years. Males outnumbered females by a ratio of 11:1. Majority of the cases occurred in the fifth decade of life irrespective of gender. Eight cases (67%) had multiple swellings seen in the attached gingiva in maxilla. Orbital and cranial involvement was found in 60% of cases and necrosis of the maxilla was present in all the cases. Restricted mouth opening was seen in 70% of cases. Hypertension was seen in 25% of cases and there was a 91% incidence of diabetes mellitus. Fatality was seen in two cases.

Conclusion

With the cumulative clinical data collected from the following 12 cases a positive identification of mucormycosis following COVID-19 was made. The risk factors associated with the disease were identified as diabetes mellitus, COVID infection, hospitalization and also the steroid therapy involved in the treatment protocol of COVID-19 patients. Early diagnosis of the disease could improve the chance of survival of the patients.

Key words : COVID-19 , coinfections, diabetes mellitus, fungal infections, maxilla, mucormycosis, post-COVID infections

Introduction

In late 2019, an enveloped acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is a single-stranded RNA betacoronavirus of the Coronaviridae family, emerged from Wuhan, China, posing global health and economic threats[1]. The World Health Organization (WHO) designated it as a pandemic disease and named it coronavirus disease 2019 (COVID-19). Despite global containment and quarantine efforts, the number of studies about the disease's epidemiological and clinical characteristics have skyrocketed [1.2]While typical clinical signs of the disease, such as dry cough, coryza, sore throat, dyspnea, myalgia, and fatigue, have been identified , there have also been reports of unusual symptoms and signs of COVID-19 infection (2). In severe cases, respiratory failure develops, leading to acute respiratory distress syndrome (ARDS), which is characterised by multiorgan failure that affects renal and cardiac function, as well as death [3].Although the cause is not quite clear, patients with severe COVID-19 are at a similar risk of invasive fungal infections as patients with severe influenza. Prevalence of fungal infections in seriously ill COVID-19 patients have been noted globally. More cases of putative oropharyngeal candidiasis (OPC) in seriously ill COVID-19 patients, especially those with low lymphocyte counts, plasmapheresis, or total parenteral nutrition (TPN) were also observed [4.5]

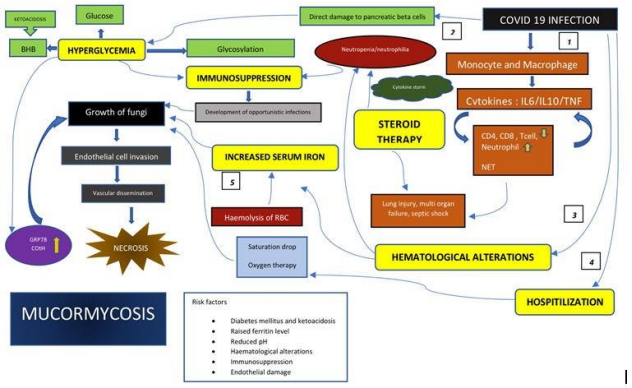
Mucormycosis is a life-threatening infection caused by fungi of the class Zygomycetes, order Mucorales. Mucormycosis is a rare opportunistic fungal infection characterised by host tissue infarction and necrosis caused by hyphae invasion of the

vasculature. Mucormycosis occurs at a rate ranging from 0.005 to 1.7 per million people [6]The global case fatality rate for mucormycosis is 46%[7]. Early diagnosis and care are critical, as even a 6-day delay in diagnosis and treatment doubles 30-day mortality from 35% to 66%. The most common clinical manifestation of mucormycosis is rhino-orbital-cerebral infection, which is thought to be secondary to spore inhalation into a susceptible host's paranasal sinuses. Patients with diabetes mellitus account for 70% of rhino-orbital-cerebral mucormycosis cases, with the majority of them developing ketoacidosis at the time of presentation. Acute sinusitis, fever, nasal congestion, purulent nasal discharge, and headache are common symptoms of infection[8.9]. Paranasal sinuses become infected and clinical effects arise from contiguous spread to neighbouring structures such as the palate, orbit, and brain. Obtundation occurs when an infection spreads from the ethmoid sinus to the frontal lobe. Diabetes, systemic corticosteroid use, neutropenia, hematologic malignancies, stem cell transplant, and immunocompromised individuals are known risk factors for mucormycosis. In immunocompromised patients, a strong suspicion for this disease must be considered. COVID-19 patients with trauma, diabetes mellitus, GC use, HM, prolonged neutropenia are more likely to develop mucormycosis [8]Preventing morbidity in this often fatal condition requires high clinical suspicion and early surgical debridement.

The diagnosis of mucormycosis is challenging and treatment should start as early as possible in order to decrease mortality. Early diagnosis of mucormycosis is of utmost importance as studies have shown that it increases survival and it may also reduce the need for or extent of surgical resection, disfigurement and suffering [10]. In clinical practice, laboratory diagnosis of mucormycosis includes histopathology, direct examination of wet mounts and culture. A definitive diagnosis is based on the demonstration of fungal hyphae typical for mucormycetes in biopsies of affected tissues. For a rapid presumptive diagnosis of mucormycosis direct microscopy of KOH wet mounts can be used. Culture of specimens is essential for the diagnosis of mucormycosis since it allows identification to the genus and species level, and eventually antifungal susceptibility testing [8.9.11]

The chances for recovery from mucormycosis are low, despite early diagnosis and intensive combination surgical and medical therapy and the mortality of mucormycosis remains high. Treatment includes antifungal agents in combination with surgical intervention. The only new agent with activity against mucorales is isavuconazole, but it does not seem to offer significant advantages over historical first line therapy of amphotericin B-based drugs or posaconazole [12]. Many researchers are hoping to find new methods for making the diagnosis of mucormycosis earlier, as early diagnosis of mucormycosis leads to improved survival. The aim of this study was to analyse the clinical features and the severity of mycotic infections in post COVID-19 patients. This case series will also outline the various fields of research targeting early diagnosis, as well as understanding the pathogenicity involved in the disease and the risk factors associated with providing knowledge to physicians to look out for the disease much earlier.

Figure1.1:represents the possible hypothesis if post covid mucormycosis. 1- On the onset covid infection, inflammatory response sets in causing cytokine storm leading to organ damage This requires steroid therapy which in turn causes immunosuppression and paves way to opportunistic infections. 2-Severe covid infection requires hospitalization where they require oxygen supplementation in the event of saturation drop. Oxygen favors the growth of aerobic organisms. 3- Covid infection directly affects pancreatic beta cells and causes hyperglycemic states. Hyperglycemia with BHB and glycosylation together causes immunosuppression and also enhances the expression of GRP78 and COtH receptors thereby enhancing the growth of fungi. 4- Inflammatory responses in covid infection can cause hematological alterations like neutropenia causing immunosuppression thereby giving way for opportunistic infections. 5- Increased serum iron from enhanced glycosylation and also hematological alterations can provide a suitable environment for the growth of fungi. All these pathways are aimed at favouring and increasing the growth of fungi. As the fungi grows, there is endothelial cell invasion causing vascular dissemination and ultimately necrosis occurs causing mucormycosis.



Materials And Methods

The study included all cases of zygomycosis that were diagnosed and treated over a 6 months period. The clinical data and laboratory findings were retrieved and analysed. All patients had active infection with a history of COVID-19. The data was analyzed for age, gender, site, symptoms and treatment including the underlying systemic complications and COVID status and follow up of patients. The tissue samples sent for diagnosis were examined grossly and processed as for routine paraffin sections. These tissue preparations were stained with Hematoxylin and Eosin (H and E), Periodic acid - Schiff (PAS). Cytologic material where available, was sent in the form of fine needle aspiration cytology or scrape smears for KOH examination. Based on these cumulative data, the severity of the disease was studied, pathogenicity analysed, early signs and symptoms identified and a possible hypothesis was attempted.

Results

Clinico- Demographic Profile

The study yielded 12 cases of mucormycosis. The age of occurrence was in the range of 30 - 60 years . Males outnumbered females by a ratio of 11:1. Majority of the cases occurred in the fifth decade of life irrespective of gender. Major risk factors included uncontrolled diabetes and COVID-19 positivity with concomitant steroid use in patients. Most cases were seen in maxilla (11 cases, 92%) in contrast to only one case in mandible (8%). The site commonly involved was the maxillary region and the orbit and it was mostly seen on the right side. Eight cases (67%) had multiple swellings seen in the attached gingiva in maxilla. Hypertension was seen in 25% of cases and there was 91% incidence of diabetes mellitus.

Table 1.1: Represents the clinical features of post- covid cases

SNo	Gender	Age	Covid history	Comorbidities	Intraoral features	Extraoral features	Final diagnosis	Treatment done And Follow up
1	Female	55	Post covid 3 months	Diabetes mellitus	Mouth opening reduced to 10mm Painful ulcers and crustaceans on lower lip Erythematous and tense swelling observed from the right infraorbital region the right lower mandible.	Necrosis extended to the orbit and cranium and maxillary mass observed.	Histopathological diagnosis Mucormycosis	Surgical debridement of necrotic bone. Right maxillary and orbital decompression I&D done Patient deceased
2	Male	45	Post covid 1 month	Hypertension and Diabetes mellitus	Necrosis seen in the roof of hard palate Mouth opening restricted to 20 mm	Swelling extending to orbit, necrosis seen in the maxillary and orbital region Loss of vision in left eye	Histopathological diagnosis Mucormycosis	Endoscopy assisted debridement and periorbital decompression. Left lid sparing orbital externation Debridement of necrotic bilateral maxilla done and BIPP patch placement
3	Male	57	Post covid 1 month	Diabetes mellitus, coronary artery disease and Severe anemia	Swelling present on the hard palate	Necrosis extendin g to orbital region	Histopathological diagnosis Mucormycosis	I&D done in palatal region Patient on palliative care owing to severe complications Patient deceased
4	Male	47	Post covid 1 month	Diabetes mellitus	Periapical abscess seen in relation to 14	Diffused swelling present on the right side of face extending from the	Histopathological diagnosis Mucormycosis	Right hemimaxillectomy done and started on antifungal therapy

						innercanthus of the eye to the malar region.		
5	Male	45	Post covid 1 month	Diabetes mellitus	Multiple swellings seen in the anterior maxillary region. Sinus opening in relation to attached gingiva of 13-23. And restricted mouth opening.	Swelling seen in relation to maxillary sinus and periorbital region and greenish bkack nasal turbinate.	Histopathological diagnosis Mucormycosis	Started on antifungal therapy
6	Male	32	Post covid 1 month	Diabetes mellitus	Inflammation and sinus opening in hard palate in relation t025,26	Periorbital swelling on right side of face	Cytopathological diagnosis Mucormycosis	Started on antifungal therapy
7	Male	55	Post covid 1 month	Diabetes mellitus and hypertension	Inflammation seen in relation to 16,17 with sinus opening in attached gingiva	No extra oral findings	Histopathological diagnosis Mucormycosis	Started on antifungal therapy
8	Male	61	Post covid 1 month Moni	Diabetes mellitus	Multiple abscess in the right maxillary vestibule region.	Right facial swelling seen	Histopathological diagnosis Mucormycosis	Right hemimaxillectomy done and started on antifungal therapy
9	Male	58	Post covid 8 months	Diabetes mellitus and chronic renal disease	Bony exposure seen in relation to 12 to 25	No findings	Histopathological diagnosis Fungal osteomyelitis with Mucormycosis	Surgical sequestrectomy followed by antifungal therapy
10	Male	55	Post covid 2 months	Diabetes mellitus	Gingival swelling with perforated bone in relation to 16 to 12 with palatal perforation seen.	No findings	Cytopathological diagnosis Mucormycosis	Started on antifungal therapy
11	Male	42	Post covid 1 month	Diabetes mellitus	Gingival swelling in relation to 14, 15	No findings	Histopathological diagnosis Mucormycosis	Maxillectomy followed by antifungal therapy
12	Male	31	Post covid 2 months	No known history	Gingival swelling in relation to 12 to 15	No findings	Histopathological diagnosis Mucormy	Started on antifungal therapy
					region		cosis	

Histopathological and Cytological Characteristics

All 10 cases were histopathologically diagnosed as mucormycosis. The characteristic hyphae of mucormycosis , which were broad, ribbon-like and predominantly aseptate with wide-angle branching, were visualized with H and E stains. Of 12 cases, four showed mild fungal load, eight moderate load. The load was found to be more in the areas of necrosis. In cases of granulomatous inflammation, the number of fungal filaments within the granulomata were few. Granulomatous inflammation noted in 6 cases (50%) were composed of macrophages and lymphocytes with central necrosis. The fungal hyphae were identified in the necrotic areas. Neutrophilic infiltration was mild in 6 cases and moderate to marked in 3 cases. All the 12 (100%) cases of mucormycosis showed tissue necrosis. Necrosis was classically pale basophilic with minimal inflammatory response and fungal hyphae were distinctly seen in it. Angioinvasion was seen in 1 (8%) of the 12 patients.. The fungal hyphae were identified in the wall of the blood vessels or forming thrombi at foci with necrosis of adjacent tissue. Bone invasion was noted in 9 (75%) cases where the hyphae localized within the bone marrow. There was also evidence of empty lacunae devoid of osteoblast suggestive of osteomyelitis in 2 cases (16%). Other 2 cases were cytologically diagnosed as mucormycosis using KOH mount. There were branch-like tubular structures refractile under light microscopy suggestive of fungal hyphae which were non septated and presented with varying lengths.

Treatment and Follow up

Maxillectomy was done in three cases, maxillary sequestrectomy in one patient, surgical debridement and decompression of maxilla and orbit in two cases . All these cases were followed up with antifungal therapy . Non surgical management was done in six cases. The treatment modality antifungal therapy with amphotericin. Fatality was seen in two cases.

Figure:1.3 Case -3

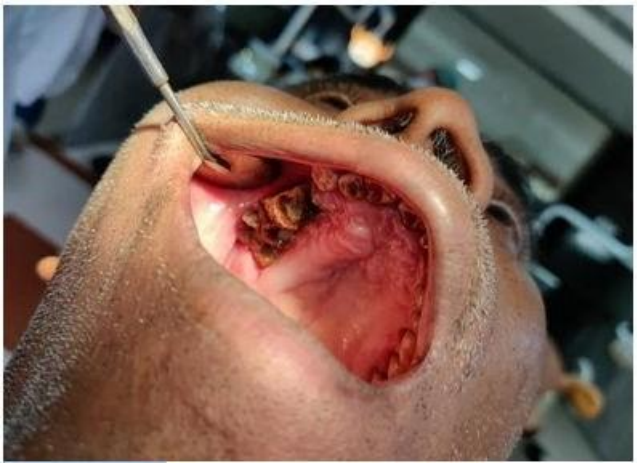


Figure: 1.4 Case-4

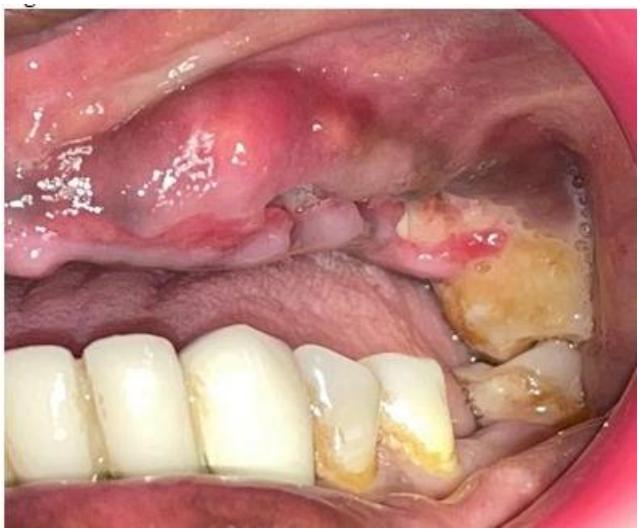


Figure: 1.5 case 9

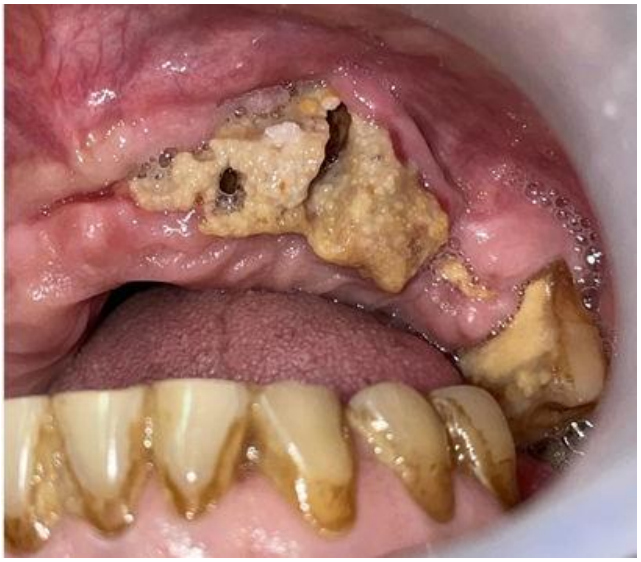
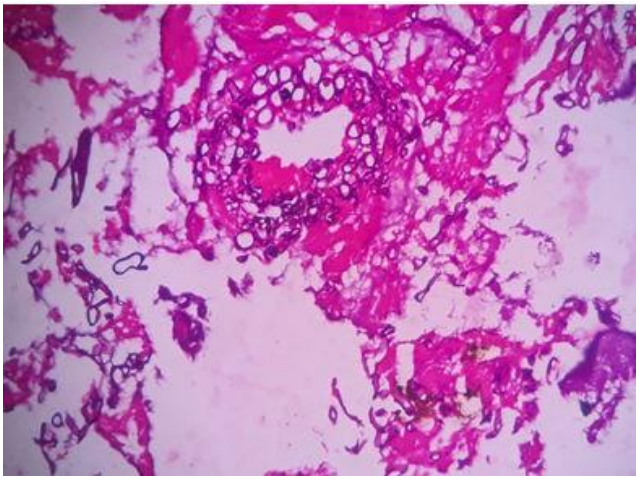


Figure: 1.6 Angioinvasion seen in case 9



Discussion

Coronavirus disease 2019 (COVID-19) has been sweeping the globe, caused by the extreme acute respiratory syndrome

coronavirus 2 (SARS-CoV-2). SARS-CoV and SARS-CoV-2 belong to the same genus, according to studies, and have similar prevalence, molecular, and clinical characteristics. In 2003, the prevalence of fungal infection in SARS patients was 14.8–27 %, and it was even higher in seriously ill patients upto 21.9–33 % [1] Also, fungal infection was the leading cause of death in SARS patients, accounting for 25–73.7 % of all causes of death [1.13] Furthermore, over the last decade, there have been an increase in cases of serious influenza pneumonia resulting in ARDS complications [14].

There have been few studies explicitly designed to look at superinfections by bacteria, fungi, or other viruses in COVID-19 patients to date. Also, published reports provide minimal data on superinfections could be possible due to the fact that most studies are retrospective. In addition, to prevent personnel exposure to SARS, most health facilities have reduced routine diagnostic procedures such as bronchoscopies, induced sputum collection, necropsy, and microbiological tests.Around 5–30% of COVID-19 patients become seriously ill and need admission to an intensive care unit [14,15] . ICU patients, especially those on mechanical ventilation, are more susceptible to bacterial and fungal infections, as is well known [14]As a result, it's important to keep in mind that COVID-19 patients may get more fungal infections in the middle and later stages of the disease, particularly if the disease is already [15]. In this study , 10 cases were analysed having post COVID mucormycosis and the reason behind it could be use of corticosteroids, diabetes mellitus and alteration of the oral microbial flora drastically allowing the commensals to become pathogenic (12).

In our case series, 11 cases were known cases of diabetes mellitus. It has been previously reported that diabetes mellitus is greatly associated with mucormycosis suggesting that chronic inflammation, increased coagulation activity, immune response impairment and potential direct pancreatic damage could be the reason behind [16].Also studies show that COVID-19 infection directly causes damage to pancreatic beta cells thereby causing hyperglycemic state. Such patients have decreased granulocyte phagocytic ability with altered polymorphonuclear leukocyte response. Zygomycetes have a strong affinity for blood vessels, can penetrate quickly, and spread widely. In diabetic patients zygomycetes produce the enzyme ketoreductase, which allows them to utilize the patient's ketone bodies [17].These findings likely explain the unique susceptibility of diabetic ketoacidosis to mucormycosis. Also, mucorales have previously been shown to bind, infiltrate, and harm human umbilical vein endothelial cells in vitro. GRP78 (glucose-regulated protein 78) is a receptor that increases mucorale's ability to penetrate endothelial cells lining blood arteries, according to a recent study. Increased glucose levels, similar to those found in diabetic ketoacidosis, increase GRP78 expression and as a result, endothelial cell invasion and injury occurs in a receptor-dependent way [18].Additionally, uncontrolled diabetes mellitus, because of ketoacidosis, can also alter the normal immunologic response of patients to infections paving way for opportunistic infections. Furthermore, mucormycosis tissue lesions are characterised by hemorrhagic necrosis [16,19]This was in accordance with our study where most of the cases had presented with diabetes mellitus. One case included in the study did not have a history of diabetes mellitus. A few studies show that COVID-19 infection could directly affect the pancreatic cells thereby causing a hyperglycemic state which could possibly favour the fungal growth [20]. Also, steroid therapy could be an adjuvant factor for the development of mucormycosis.

Of the 12 cases, the common signs and symptoms observed were pain and swelling in the maxillary and orbital region. Maxillary necrosis was observed in all the cases where increased coagulation activity could be seen in COVID-19 patients as quoted by Hussain et al, 2020 **(21)**. Maxillary bone is involved more because of the presence of maxillary **(22)**. The damp or the moistened environment of the maxillary sinus facilitates harbouring and growth of the fungi thereby making maxilla the most affected region in mucormycosis **(23)**. Mucormycosis of the head and neck region results from inhalation of airborne spores. In the nasal mucosa, germination ensues and the hyphal elements penetrate, by direct extension or through vascular channels, the paranasal sinus, orbit and the brain and occasionally even the eye **(24)**. This could be the explanation for the maxilla being affected in all the cases with the mandible being spared . Interestingly, eight cases (67%) presented with multiple swellings in the attached gingiva of maxilla. Though soft tissue didn't yield any confirmation of mucormycosis, biopsy of the bone revealed the presence of fungi. This type of clinical presentation could be suggestive of early diagnosis of mucormycosis. Timely initiation of treatment improves the outcome of mucormycosis. Similarly, early treatment is predicated on early diagnosis. Early diagnosis of mucormycosis is important, and prompt therapeutic intervention may prevent progressive tissue invasion and its sequelae.

All the 12 patients were under steroid therapy for COVID-19 infection. It is known that corticosteroids have been proven to be a predisposing factor for mucormycosis as quoted by Anna Skiada et al **(25)**. Severe COVID-19 patients are faced with a twofold problem. On one hand, there is the hyperinflammatory response, resulting in pulmonary thrombosis, extravasation of cell debris and acute lung injury or even ARDS . On the other hand, there is a need to clear the viral infection itself **(26)**. This primary phenomenon suggests a possible target for corticosteroids. The anti-inflammatory properties of steroids reduce systemic inflammation, exudative fluid in lung tissue, and prevent further diffuse alveolar damage, improving hypoxia and lowering the risk of respiratory failure **(27)**. The worsening of dysglycemia/unmasking of latent diabetes is a possible side effect of corticosteroid therapy. By directly interfering with the signalling cascade of the GLUT-4 receptors, corticosteroids cause increased lipolysis, increased hepatic glucose output, and can increase insulin resistance by up to 60%–80% . This results in a 30–50% decrease in insulin-stimulated glucose uptake by skeletal muscle cells, contributing to postprandial hyperglycemia, as well as a 50–70% decrease in hepatic glycogenesis **(28)**. This was applicable to the cases in our study as all were reposted diabetic. It is also evident that corticosteroids can cause impairment in the migration, ingestion and phagolysosome fusion of bronchoalveolar macrophages **(29)**. Coupled with the potential adverse effect of steroid-induced hyperglycemia, a diabetic patient receiving corticosteroids is exceptionally vulnerable to the development

of mucormycosis. Several studies also show that long term use of high dose steroids alter the immune response and suppress the immunity of the patient making them susceptible to co-morbid infections **(30)**. These findings could possibly explain the morbidity involved in post COVID fungal complications as observed in our study.

Recent studies also have deciphered the role of ferritin in mucormycosis. Virtually all microbial pathogens require iron for growth and virulence. As serum iron is highly bound to carrier proteins like transferrin in mammalian hosts, microorganisms have very little access to it. Because of the release of iron , patients with diabetic ketoacidosis have higher levels of available serum iron (20). Artis et al (31) showed that sera collected from patients with diabetic ketoacidosis supported growth of Zygomycetes in the presence of acidic pH . Serum iron could also be accumulated because of hematologic alterations like neutropenia because of RBC breakdown and subsequent heme accumulation. When intracellular iron concentration rises, iron is stored in the form of ferritin and then expelled from the cell, resulting in ferritin production (32). Ferritin is not only linked to inflammation, but it may also be a direct indicator of cellular damage, particularly when it exceeds 600ng/mL, implying a link between organ damage and ferritin formation (33). Hyperactivation of this process results in cell death, known as ferroptosis (33,34). This could also be one of the possible pathogenesis in COVID patients who are more susceptible to mucormycosis and the fatality of the condition could be explained as well.

COVID-19 also has been related to immune dysregulation, which affects both Th2 and Th1 responses, as well as the cytokine release syndrome, which causes lung pathology and encourages pulmonary microbial proliferation and infection (35). Intensively sick COVID-19 patients have higher levels of both pro-inflammatory (IL-1, IL-2, IL-6, tumour necrosis factor alpha) and anti-inflammatory (IL-4, IL-10) cytokines, as well as fewer CD4 and CD8 cells. This could give rise to haematologic alterations like neutropenia and/ or neutrophilia causing immunosuppression. Invasive fungal infections are more likely in this extreme clinical situation. All the 12 cases included in the study had been hospitalized owing to severe COVID-19 infection. All patients were on supplemental oxygen therapy owing to respiratory difficulties and saturation drop. This could also possibly give rise to nosocomial infections and also increased oxygen favours the growth of fungi being aerobic thereby causing endothelial invasion and subsequent necrosis. On the follow up of the cases, case 1 and case 3 had been deceased. Balaji et al, 2020 had previously stated that fungal infections have been proven deadly and known to have a fatality rate of more than 40% , thus correlating with the fatality observed in our patients.

From these results, it is evident that mucormycosis is a fatal complication of COVID-19 and diagnosis of mucormycosis remains challenging. However, early diagnosis of mucormycosis can improve the chance of survival as mentioned in previous studies. Therefore it is suggested that it is prudent to assess the risk factors, the types of invasive mycosis, the strengths and limitations of diagnostic methods, clinical settings, and the need for standard or individualized treatment in COVID-19 patients and finally provide a clinical picture to assist the clinicians and laboratory experts in the management of mucormycosis, as a comorbidity in COVID-19 patients. As an emerging condition in COVID patients, mucormycosis is now being seen widely and the accumulation of these case details posed a challenge. With the knowledge gained and understanding the fatality of the disease a hypothesis was postulated. Future studies can be done for better understanding of post COVID fungal complications, it's early symptoms and its treatment.

Conclusion

With the cumulative clinical data collected from the following cases a positive identification of mucormycosis following COVID-19 was made. Also, a unique clinical presentation of multiple gingival swellings in the maxilla could possibly indicate an initial sign of mucormycosis thereby paving way for an early diagnosis of the disease. Physicians should maintain a high degree of suspicion for possible invasive fungal infections, including mucormycosis, in patients with underlying immunodeficiency who are receiving high-dose steroid therapy. Judicious use of steroids and early detection and treatment could improve outcomes in these patients.

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