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Review Article

Mucormycosis—A significant hazard in the COVID-19 pandemic?

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ABSTRACT

Mucormycosis was the third most common angio-invasive fungal infection after candidiasis and aspergillosis. However, the frequency of this disease seems to be increasing with the arrival of COVID-19 infection. Despite efforts to better understand the pathophysiology of mucormycosis, its fatality rate remains high. Therefore, this review article aims to accomplish an evidence-based review answering whether mucormycosis is a significant hazard in the era of COVID-19 infection. It contains a wealth of information about the infection's aggressive and deadly characteristics in diabetic and immunocompromised individuals, as well as its pathogenesis, clinical aspects, and management, along with its link to COVID-19, which is the need of the hour.

The method used to assemble all the information was a review of the literature, along with multiple case reports supporting the occurrence of COVID-19 linked mucormycosis.

This article concludes that uncontrolled diabetes mellitus in COVID-19 patients makes them more vulnerable to secondary infections, primarily mucormycosis, due to the over-zealous use of corticosteroids for its treatment, resulting in immunosuppression. The diagnosis and treatment of this black fungus have also been established to be quite challenging.

The effective management of mucormycosis in immunocompromised individuals is centered on a multimodal approach that includes early diagnosis, or cessation of the primary prompting factors, administration of antifungal agents at ideal doses, and comprehensive amputation of all devitalized tissues, along with several adjunctive remedies.

1. Introduction

Coronavirus disease is a viral infection caused by severe acute respiratory syndrome coronavirus-2 (SARS-COV-2).[1] The symptoms include mild to life-threatening pneumonia, along with many co-infections such as oropharyngeal candidiasis, pneumocystis jirovecii pneumonia, pulmonary aspergillosis, and bloodstream candida infections.[2,3] Moreover, cases of rhino-orbital-cerebral mucormycosis were reported in greater frequency post-COVID-19 infections which were earlier an occasional finding.[3,4]

Mucormycosis represents as the most common angio-invasive fungal infection after aspergillosis and candidiasis.[5] It is an infection caused by filamentous molds of the order Mucorales and Entomophthorales.[6] These two orders produce vividly different contagions.

Early documentation of the high-morbidity situations is vital for its optimal treatment.[1]

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2. Incidence & Epidemiology

The incidence rate of mucormycosis is rare but in the past two decades, it has increased worldwide, particularly in India, France, Switzerland, and Belgium.[7] Mucormycosis post-COVID-19 has been reported from all over the world, but mucormycosis alone establishes a minor percentage of infections.

Universally, the prevalence of mucormycosis varied from 0.005 to 1.7 per million population, although for the year 2019-2020, India was accountable for the highest cases of mucormycosis in the world.[8,9] In every aspect, diabetes mellitus is the foremost risk factor associated with mucormycosis, with an overall mortality of 46%.[10]

388 cases of mucormycosis were confirmed in a 2019 national multi-center study in India before COVID-19.[11] According to Prakash et al.[11] research, 18% of patients had diabetic ketoacidosis, and 57% had uncontrolled diabetes mellitus. Similar to this, Patel et al.[12] reported data on 465 cases of mucormycosis without COVID-19 in India and came to the conclusion that rhinoorbital mucormycosis (67.7% of patients), pulmonary mucormycosis (13.3%), and cutaneous mucormycosis (10.5%) were the most common presentations. Malignancy (9.0%), organ transplantation, and diabetes mellitus (73.5%) were shown to be Indians' most common risk factors (7.7 percent).[12]

In a recent systematic review conducted until April 9, 2021, John et al.[13] reported 41 confirmed cases of mucormycosis in people with COVID-19, 93% of cases reported diabetes mellitus, while 88% has a history of undergoing corticosteroid therapy. These findings are comparable to a case series of 101 COVID-19 associated mucormycosis patients, in which 80 percent of individuals had diabetes mellitus and more than two-thirds were treated with corticosteroids. They suggest a profane trinity of diabetes, mucormycosis, and steroid in COVID-19 patients.[5]

To summarize, mucormycosis remains rare, but COVID-19-related mucormycosis has intensely altered the broad understanding.

3. Pathogenesis

There are several studies about the pathogenesis of mucormycosis but hardly any of them explains the pathogenesis of COVID-19 associated mucormycosis, hence there are many questions to be answered.

To begin with the pathogenesis of mucormycosis, studies have shown that Mucorales can gain entry to a susceptible host through various ways such as breath, absorption of polluted food, or chafed skin. Rhizopus grows quickly in a hyperglycemic environment because phagocytosis is significantly impaired in a high sugar state.[14] The ketone reductase system in them helps to efficaciously survive the acidotic environment in diabetic ketoacidosis.[14]

Invasive mucormycosis has been observed in patients with mild to moderate SARS-CoV-2 infections. COVID-19's pathophysiologic features allow for secondary fungal infections and a proclivity to cause extensive pulmonary disease, as well as subsequent alveolo-interstitial pathology, which increases the risk of invasive fungal infections.[15] The main reason that Mucorales spores germinate in people with COVID-19 is an ideal environment of hypoxia, high glucose (diabetes, new-onset hyperglycemia, steroid-induced hyperglycemia), acidic medium (metabolic acidosis, diabetic ketoacidosis [DKA]), increased ferritins, decreased numbers of T-lymphocytes, CD4+T, and CD8+T cells (altered innate immunity).[5,16]

Continuing use of corticosteroids has always been associated with opportunistic infections such as aspergillosis and mucormycosis, but even a brief introduction of these (5-14 days) has lately been reported, especially in people with Diabetes Mellitus.[5] This therapy is used as part of the treatment regimen for people infected with Covid-19. They reduce neutrophil migration, ingestion, and phagolysosome fusion. When combined with the potential consequences of steroid-induced hyperglycemia, diabetic COVID-19 patients receiving corticosteroids or other immunosuppressive drugs are especially vulnerable to the development of mucormycosis.[15] Immunocompromised people are at risk of mucormycosis if they have received more than 600 mg cumulative prednisone or a total methyl prednisone dose of 2-7 g in the previous month.[17] The majority of patients in a study conducted by the European Confederation of Medical Mycology[18] had received corticosteroids within a month of being diagnosed.

Several causes that may precipitate mucormycosis in individuals with COVID-19 are as follows:[5]

1. The presence of diabetes mellitus with or without Diabetic ketoacidosis increases the risk of mucormycosis and is associated with an amplified severity of COVID-19. Uncontrolled hyperglycemia and precipitation of diabetic ketoacidosis are often observed due to corticosteroid intake.[15] There is increased expression of the endothelial receptor glucose-regulator protein (GRP-78), resulting in polymorphonuclear dysfunction, impaired chemotaxis, and defective intracellular killing[15] and the Mucorales adhesin spore coat protein homologs (CotH), generating a "perfect storm" for intensified adhesion and penetration to the endothelium enabling angioinvasion, hematogenous dissemination, and tissue necrosis.[19]
2. Low pH due to acidosis is a fertile medium for mucor spores to germinate. Moreover, steroid use reduces the phagocytic activity of WBC, and causes impairment of broncho-alveolar macrophages migration, ingestion, and phagolysosome fusion, making a diabetic patient

exceptionally vulnerable to mucormycosis. In healthy individuals, mononuclear and polymorphonuclear phagocytes eliminate fungal species and hyphae of the oxidative and non-oxidative killing mechanisms.[20] If macrophage function is impaired, these cells may fail to clear the spores permitting their germination into hyphae,[21] causing local invasion and tissue destruction.

3. Another possible explanation is "endothelialitis" observed in severe COVID-19.[22]
4. An important virulence trait of mucorales is the ability to acquire iron from the host which is an essential element for its growth.[23] In conditions of ketoacidosis, free iron becomes accessible in the serum. Hyperglycaemia diminishes iron-binding allowing increased free iron. Mucorales further increase their virulence by taking up this surplus endogenous iron through siderophores or iron permeases.

   Moreover, an increase in cytokines in patients with COVID-19, especially interleukin-6, due to severe infection and diabetic ketoacidosis, stimulates ferritin synthesis and downregulates iron export resulting in intracellular iron overload, further exacerbating it.[23] Furthermore, concomitant acidosis and tissue damage leading to an increase in free iron in the circulation[24] and, additionally, reduce the ability of transferrin to chelate iron.
5. Although rare, nosocomial outbreaks of COVID-19-Mucormycosis have been linked to contaminated dressings, medical apparatus, and ventilation system.[25,26]

Elegant discussions of pathogenesis are published elsewhere.[27,28]

4. Clinical Features

Clinical manifestations of Mucormycosis can be classified by the tissue site affected in forms like (i) Rhino-orbital-cerebral[29] (ii) Pulmonary[30] (iii) Cutaneous/soft tissue[31] (iv) Gastrointestinal[32] (v) Disseminated[30,33] (vi) Uncommon sites.[34] All Mucorales species produce clinical images that are similar.

4.1. Rhino-orbital-cerebral mucormycosis

The rhino-orbital-cerebral disease is the most common form of mucormycosis.[35] It is a rare invasive fungal infection that originates in the paranasal sinuses and may frequently extend into the orbits and cerebral parenchyma.[36] In this type, it invades the sinuses and extends into the palate, oral mucosa, bone, orbit, and brain. Uncontrolled diabetes mellitus and the use of corticosteroids for the treatment of respiratory symptoms are possible etiological factors[36] being more common in patients with poorly controlled DM[33,37] but may occur in SOTRs[38] and other immunocompromised hosts.[33]

The infection in rhino-orbital-cerebral mucormycosis can spread directly into the paranasal sinuses and then invade the orbital and intracranial spaces via direct spread or the bloodstream.[21] It can present with common signs and symptoms like fever, lethargy, headache, orbital pain, abrupt loss of vision, and can extend to atypical signs and symptoms similar to complicated sinusitis, such as nasal blockage, crusting, proptosis, facial pain, and edema, along with facial palsy, peri-orbital cellulitis, epistaxis, trigeminal nerve disturbance, and sensory loss and seizures, and even ophthalmoplegia and various other neurological signs and symptoms of intracranial extension.[39] Progression from the sinuses into the mouth often occurs, eventually producing a painful black necrotic eschar. It is often seen in the nasal cavity or over the hard palate region, but it is not a characteristic feature.[40] Extension of the disease into the brain can progress by the optic nerve or through the venous drainage of paranasal sinuses by the cavernous sinus.[24] For a favorable ROCM outcome, rapid and aggressive treatment with combined surgical debridement/resection and medicinal therapy is required.[37,41]

Veisi et al.[42] concluded that COVID-19 and the related short-term corticosteroid therapy were the only predisposing factors conducting the patient to rhino-orbito-cerebral mucormycosis in one of his cases. This indicated that in the presence of COVID-19 even short-term corticosteroid therapy can predispose the patient to mucormycosis. In another case, they[42] reported that COVID-19 and the corresponding short-term corticosteroid therapy resulted in high blood sugar followed by rhino-orbital mucormycosis. On the other hand, COVID-19 has never been reported as a predisposing factor for rhino-orbital and/or rhino-orbito-cerebral mucormycosis.[42]

4.2. Pulmonary mucormycosis

Pulmonary mucormycosis occurs commonly in neutropenic patients with cancer undertaking induction chemotherapy and those who have experienced HSCT and have graft-versus-host disease. It may occur as part of rhino-cerebral or disseminated disease. It has been identified as a secondary complication of coronavirus disease-2019 (COVID-19), particularly among critically ill patients in the intensive care unit (ICU).[43,44] According to reports, up to 35% of these patients have invasive pulmonary aspergillosis, which has been linked to prior corticosteroid use and has resulted in higher mortality.[43–45] In contrast, only two cases of invasive pulmonary mucormycosis have been reported as a result of COVID-19.[46]

It has non-specific clinical features that are difficult to distinguish from pulmonary aspergillosis. Invasion of pulmonary vessels may result in necrotizing pneumonia;[30] pulmonary arterial aneurysms; fatal aortic rupture; and fatal

hemoptysis.[47] Radiographic findings are varied and not specific but help localize and define the extent of disease to perform an adequate diagnostic procedure.[48,49]

4.3. Cutaneous / soft tissue mucormycosis

Cutaneous Mucormycosis is caused by the phylum Glomeromycota opportunistic fungi.[50] It is common in poorly controlled diabetic patients and immunocompromised individuals, and is usually acquired through direct inoculation through trauma.[50] Patients with cutaneous mucormycosis are more likely to have skin barrier disruptions (burns, trauma, catheter insertion, injections) or persistent skin maceration.[27] The skin is infected, with the arms and legs, face, scalp, thorax, back, abdomen, perineum, breast, neck, and gluteal area being the most affected.[51] Although secondary vascular invasion and hematogenous spread are rare, the fungus can invade adjacent fat, muscle, fascia, and even bone.[33] The skin is infected by direct inoculation in primary disease, and by dissemination from a rhinocerebral infection in secondary disease.

Its onset may be gradual, and it may progress slowly, or it may be fulminant, leading to gangrene and hematogenous dissemination.

Broad careful debridement, hostile to parasitic treatment, remedy of the basic metabolic or weakened immunological status, and control of other attending contaminations are important to further develop endurance in cutaneous mucormycosis.[50] Death paces of limited cutaneous Mucormycosis are lower contrasted with other types.[52]

4.4. Gastrointestinal mucormycosis

It is a relatively uncommon disease that is seen in the stomach, followed by the colon and ileum.[53] Usually, it is seen in premature neonates, often in association with widely disseminated disease. Other rare cases of it were described in association with other immunocompromised conditions, including AIDS, systemic lupus erythematosus, and organ transplantation.

These are generally acquired by ingestion of pathogens in foods such as fermented milk and dried bread products.[54] The intestinal wall may rupture and cause peritonitis which may be fatal.[55] Non-specific abdominal pain and tightness associated with nausea and vomiting are the most common symptoms.Antifungal medication alone is ineffective in controlling it; surgery is required to de-bulk the fungal infection and/or resect all contaminated tissue for a complete cure. While gastrointestinal mucormycosis is unusual (about 8% of cases), the stomach and colon are the most commonly affected organs, with mortality rates as high as 85%.[33]

A critical provisional diagnosis of invasive mucormycosis is, therefore, necessary for post-COVID-19 patients presenting with mesenteric ischemia or bowel perforation especially if they were diabetic or used high-dose steroids.[56]

4.5. Disseminated mucormycosis

The lung is the most commonly associated organ with disseminated mucormycosis. It is having a high mortality rate that occurs in severely immunocompromised patients.[57] Roden et al. study states that the mortality rate of disseminated mucormycosis is 96%.[33] when the disease had disseminated.[58] Early detection relies heavily on the presence of a metastatic skin lesion.

4.6. Uncommon forms

Intravenous drug use is the typical risk factor for uncommon or unusual mucormycosis. It includes endocarditis, osteomyelitis, peritonitis, and pyelonephritis.

5. Diagnosis

The diagnosis of mucormycosis depends upon histopathology and culture. The gold standard for the clinical diagnosis of mucormycosis is the 1950 Smith and Krichner[59] criteria. (Diagram 1)

Diagram 1: 1950 Smith and Krichner criteria

In addition to this, radiographic imaging and clinical signs and symptoms help in diagnosis. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) show a lack of enhancement in areas of devitalized sinus mucosa. These CT and MRI are often non-specific findings, it may be difficult to distinguish mucormycosis from other sino-orbital conditions. However, once the confirmatory diagnosis has been made, CT and MRI can help to delineate the extent of infection and can guide surgical debridement.[60]

Samples from the infection site are required to make a diagnosis based on the detection of typical hyphae or

a positive culture. Millon et al. developed a quantitative multiplex polymerase chain reaction (qPCR)-based 18s rRNA targeting mucor/rhizopus and rhizomucor with the goal of detecting Mucorales DNA in the blood early in the course of the infection (serum).[61]

Potassium hydroxide (KOH) preparation is used for the rapid detection of fungal elements in a clinical specimen, as it clears the specimen making fungal elements more visible during direct microscopic examination.[51] The presence of thick-walled, aseptate, and refractile hyphae 6 to 15 micrometer in diameter, with some hyphae being swollen and distorted, is indicative of the presence of Mucorales fungi.

Staining with Grocott-Gomori methenamine-silver nitrate, periodic acid-Schiff or calcofluor white demonstrates the pathognomonic broad, irregular, non-septate, and right-angle branching hyphae.

6. Management

Treatment of mucormycosis involves a combination of surgical debridement of involved tissues and antifungal therapy.[62] Elimination of predisposing factors for infection, such as correction of hypoxia, hyperglycemia, metabolic acidosis, deferoxamine administration, immunosuppressive drugs, neutropenia, and electrolytic imbalance is also critical and needs to be undertaken.[51] Its management relies on the correction of underlying factors, aggressive antifungal therapy, and surgery when possible.

Steroids, anti-metabolites, and immunosuppressive drugs should be discontinued or be made to the lowest possible dose. Early diagnosis is crucial to promptly initiate therapeutic interventions for preventing progressive tissue invasion and its devastating sequelae, minimizing the effect of disfiguring corrective surgery, and improving outcome and survival.[63]

Intravenous (IV) amphotericin B (a lipid formulation) is the drug of choice for initial therapy. The use of a lipid formulation of amphotericin-B was advocated for mucormycosis in the 2016 recommendations from the European Conference on Infections in Leukemia (ECIL-6), as well as in the ESCMID/ECMM guidelines.[64] Aggressive surgical debridements are usually undertaken, along with high dose intravenous amphotericin-B therapy is 5 mg/kg i.v. daily and as high as 10 mg/kg/day for the infection of the central nervous system. Treatment needs to be continued until remission is achieved.[63,64]

Itraconazole and terbinafine have some effectiveness against some strains, as do posaconazole and isavuconazole. Isavuconazole is a recently developed triazole, with a wide spectrum of antifungal activity against Mucorales.[65] Rezafungin, SCY-078, orolofim, and encochleated amphotericin B are some of the latest antifungal medications being tested in clinical trials.[66]

Other adjunctive therapies include the use of hyperbaric oxygen and administration of cytokines at the same time with antifungal therapy to make an oxygen-enriched cell environment. Amphotericin B installations through the nose were well-tolerated with no reports of inflammation, irritation, pain, discharge, or epistaxis.[67] Since, amphotericin-B has poor oral bioavailability due to its low permeability and solubility, oral absorption was considered negligible, even if ingested.[68]

As part of source management and fungal load reduction, surgical debridement or reduction has critically important adjunctive roles in some patients with mucormycosis.[14,18,33,37,41] Daily repeat debridement may be needed until clinical improvement is established in rhino-orbital-cerebral mucormycosis.

Surgery was discovered to be an independent determinant for positive outcomes in patients with mucormycosis in a logistic regression model.[33] Furthermore, in many case series, patients who did not have their mucormycosis surgically debrided had a much greater mortality risk than those who did.[67]

7. Prognosis

Even with intensive surgery and intravenous antifungal medication, its prognosis is still bad. It has documented fatality rates of 33.3 percent – 80 percent in disseminated infections and 100 percent in severe cases.[39] Even the survival rate in patients with uncontrolled diabetes mellitus suffering from the rhino-cerebral form is very grave. The list of highly susceptible individuals at risk of mucormycosis is enumerated in Diagram 2.

Roden et al.[33] conducted a multivariate regression analysis of risk factors for mortality in mucormycosis and discovered that disseminated illness, renal failure, and infection with Cunninghamella species were all significant mortality risk factors.[50] Brain, cavernous sinus, and carotid artery involvement are frequently related to poor results.

8. Reconstruction and Rehabilitation

Maxillofacial rehabilitation is a multidisciplinary task and pre-surgical discussion with operating surgeons is indispensable to discover the likelihood of creating favorable tissue undercuts to retain the prosthesis.[69] It is a challenging assignment, but results in improved function, aesthetics, and comfort to the patient, thus, enabling them to lead a normal life.[70] The maxillary antrum is the usual site of origin of the infection, which progressively erodes, and perforation ensues with osseous destruction and oro-antral fistula formation.

9. Conclusion

In light of the recent increase in instances of this opportunistic infection worldwide as well as at our institute,

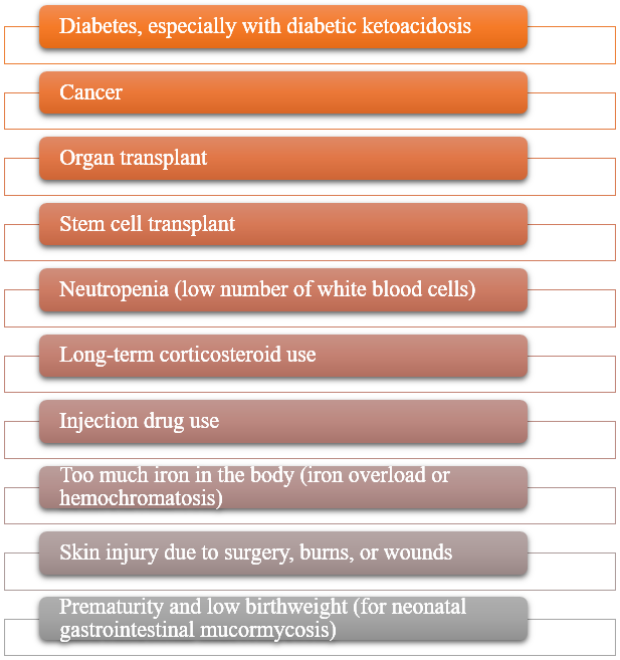

Diagram 2: Highly susceptible Individuals at increased risk of getting mucormycosis

the goal of this review is to outline the pathophysiology, clinical characteristics, and risk factors of mucormycosis to emphasize the necessity of early identification. In our experience, we treated sixteen mucormycosis cases post COVID-19 infection within 4 months. Surgical debridement was the management undertaken for all of them, yet the mortality rate observed was approximately 30%, whereas 60% of the individuals had to undergo orbital eccenteration as a part of their treatment protocol.

Because of the invasive nature of the infection and the frequent underlying malignancy, early detection is critical for the successful care of post-coronavirus disease-associated mucormycosis in people with uncontrolled diabetes and immunosuppression. Increased mucormycosis cases appear to be the result of an unlucky confluence of diabetes, excessive corticosteroid use, and COVID-19. To limit the incidence of deadly mucormycosis, all efforts should be taken to maintain optimum hyperglycemia, and only prudent evidence-based use of corticosteroids in patients with COVID-19 is advocated.

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11. Conflict of Interest

None.

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