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Covid-19-Associated Mucormycosis: An Overview of Disease Spectrum and Cases across the World

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ABSTRACT
Mucormycosis, commonly referred to as "black fungus disease," is are but serious fungal infection caused by mucormycetes group belong to the order Mucorales. The fungal infection generally occurs in severely immune compromised hosts, such as those with uncontrolled diabetes mellitus, hematologic malignancies, neutropenia, or transplant recipients. Epidemiologically, its incidence is seen more in developing countries as compared to developed ones. The coronavirus disease-2019 (COVID-19) pandemic and poorly controlled DM have increased the mucormycosis manifestations, especially in India. The exact data on the incidence and prevalence of COVID-19associated mucormycosis is unavailable due to the lack of population surveillance studies. However, documented and published case studies have reported a considerably higher incidence of rhino-orbital-cerebral mucormycosis compared to other forms during the COVID-19 pandemic. The presence of non-specific symptoms and delay in identifying them make the diagnosis of mucormycosis highly challenging. In addition, the disease progresses rapidly, and delay in treatment may markedly worsen the outcome and result in fatality.This article is a review of detailed knowledge of this disease and includes a compiled data of a few cases of mucormycosis along with their diagnosis and treatment protocols followed and reported across the world during this time.
KEYWORDS: *Diabetes mellitus; fungal infection; immunocompromised host; Rhino-orbital-cerebral mucormycosis; Zygomycosis*

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INTRODUCTION

Mucormycosisis a rare angio-invasive fungal infection caused by a group of filamentous molds/fungi called mucormycetes [1]. The disease was formerly known as zygomycosis and the common generic name of mucormycosis is "black fungus disease" [1,2]. Mucormycetes belong to the class Zygomycetes; order Mucorales and Entomophthorales with numerous genera including *Rhizopus, Mucor, Cunninghamella, Rhizomucor, Lichtheimia, Apophysomyces,* and *Saksenaea* [1, 2]. The causative agents belonging to the order Entomophthorales are highly uncommon. Under the order Mucorales, *Rhizopus* is the most common disease-causing agent followed by *Mucor* and *Lichtheimia* [3]. *Apophysomyces spp.* is commonly found in tropical and sub-tropical regions [4]. *Cunningha mella*is a highly virulent genus associated with high mortality rates [5]. These agents involve multiple organs in the body regions causing sinus, pulmonary, subcutaneous, and orbital infections [1-5]. Cumulative data suggests that mucormycosis is associated with high morbidity and mortality owing to lack of awareness, uncommon occurrence, and low incidence and prevalence [6].

Mucormycosis was first described by Fürbinger in 1876 when he observed fungal hyphae and sporangia in the hemorrhagic infracted lungs of a cancer patient during postmortem [7]. In 1885, Arnold Paltauf published the first case of "Mycosis mucorina" caused by *Lichtheimia corymbifera* that showed the presence of sporangiophores and rhizoid-like structures [8]. since then, the disease has existed. Although mucormycosis occurs rarely, the number of cases has increased in the last 2 years of the COVID-19 pandemic, with cases of the disease manifesting in large numbers particularly in covid infected individuals.

Pathophysiologically, mucorale infections occur due to inhalation of spores or sporangiospores, ingestion of contaminated food, or entry of spores via the damaged skin (cut or burn) or wounds causing traumatic inoculation [9, 10]. Upon entry, the fungal spores germinate to form hyphae in the host, which are responsible for the initiation of clinical symptoms. Morphologically and microscopically, the fungus has ribbon-like hyphae with a black–brown fuzzy appearance [5, 8, 9]. Mucormycetes grow in environmental niches such as soil, dust, bread, and decaying vegetable matter. These majorly affect immune compromised individuals with a low potential to fight infections in developed countries [10]. In contrast, in developing countries such as India, patients with poorly controlled diabetes mellitus (DM) or those with sustained trauma/malignancies are at the risk of developing this saprophytic infection [10]. These molds have the potential to invade blood vessels leading to thrombosis, necrosis, and tissueinfarction [11].

The ongoing COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected more than 130 million people and caused more than 2.4 million deaths globally [12]. It has greatly impacted the physical, social, and economic well-being of people since March 2020. Severe COVID-19 patients become immune compromised, making them susceptible to fungal infection [13]. Some of the proposed reasons for the manifestations of COVID-19-associated mucormycosis are:

1. COVID-19 is primarily associated with extensive pulmonary defects that include diffused alveolar damage, interstitial lymphocyte infiltration, hyaline membrane formation, and vascular microthrombi formation, thereby providing an environment for fungi to grow and invade airways or sinuses and invade other body tissues [13]. Nose and sinuses are primary sites of infection, from where the infection an spread to the eyes or brain resulting in blindness and seizures, respectively.
2. COVID-19 results in augmented inflammatory cytokine levels, such as interleukin (IL)-6, IL-10, and tumor necrosis factor-alpha (TNF-α), and a dysregulated immune system that may promote fungal infections [14].
3. Patients with severe COVID-19 may require mechanical ventilation and prolonged stay in intensive care units (ICUs) that could predispose them to fungal infections [15].
4. The current data on mucormycosis suggest that the prolonged use of steroids for COVID-19 management could predispose the patients to an increased risk of fungal infection. The incidence and frequency of mycosis have remarkably increased worldwide with the increased use of immunosuppressive drugs [16].
5. Mucormycosis is an opportunistic saprophytic infection that progressesvialocal colonization in the host with an impaired immune system.[12-16] In addition, mucoraleinfectionshave now emerged as a majorcause of concern in this pandemic, especially in patients with poorly controlled DM [17].

Thus, DM, the use of corticosteroids to treat COVID-19, and other co-morbidities are considered as major risk factors for the progression and development of mucormycosis. Through this article, we aim to discuss the epidemiology, clinical outcome, diagnosis, and management of COVID-19-associated mucormycosis along with reviewing the cases of mucormycosis reported worldwide.

EPIDEMIOLOGY AND PREDISPOSITION FACTORS

The epidemiologic data on mucormycosis has been derived from published case reports and case series. In 2005, Roden *et al*. analyzed 929 cases published from 1940 to 2003 [18]. In 2019, Jeong *et al*. analyzed and reviewed 851 cases published from 2000 to 2017. The data reported a higher disease burden in Europe than in Asia (34% vs. 31%), whereas the disease burden reported in America was 28% and 3% in Africa, Australia, and New Zealand [19]. These reports and the current scenario explain the increasing incidences of mucormycosis in a simplified manner. However, the exact prevalence of mucormycosis remains unknown due to the lack of population-based studies or under-reporting of cases.

Only a few population-based surveillance studies have been conducted worldwide. Being an opportunistic disease, its annual incidence was observed to be 1.7 cases per million individuals, i.e., 500 cases per year in San Francisco during 1992–1993 [20]. In France, the prevalence was 0.7 cases per million in 1997 that increased to 1.2 cases per million in 2006 [21]. Spain reported an increasing prevalence of mucormycosis from 1.2 cases per million during 1986–2006 to 3.3 cases per million during 2007–2015 [22]. Iran documented a rising trend of infection from 9.7% in 2008 to 23.7% in 2014 [23]. In India, the annual incidence of mucormycos is increased from 12.9 cases per year during 1990–1999 to 89 cases per year during 2013–2015 [24]. The estimated prevalence of mucormycosisis approximately 0.14 cases per 1,000 Indian individuals, which is nearly 70 times higher than that reported in developed countries [24]. The actual number of cases could be considerably more than the reported cases. The Leading International Fungal Education (LIFE) portal estimated the annual prevalence of the disease globally as 9,10,000 cases, whereas the disease burden is nearly 10,000 cases worldwide, excluding Indian data [25]. The epidemiological data suggest that mucormycosis prevalence was already high in India as compared to

other countries and COVID-19-associated mucormycosis worsened the situation. The Government of India reported 8,848 cases of COVID-19-associated mucormycosis until mid-May. The incidence, prevalence, and exact number of COVID-19-associated mucormycosis cases and associated death rates are still unknown [24, 26]. However, the overall increase in numbers indicates mucormycosisas an emerging disease and an alarming threat, especially in India.

Risk factors

The predisposition factors underlying mucormycosis include DM, hematologic malignancies (HM), solid organ transplantation, corticosteroids, trauma, iron overload, illicit intravenous drug use, neonatal prematurity, and malnourishment [27].

Diabetes mellitus

Patients with DM and obesity are more prone to developingsevereCOVID-19 infections and thus mucormycosis. Uncontrolled, Type IIDM, reported in 73.5% cases in India, 75% cases in Iran, and 72% in Mexico, has been seen to be a major risk factor forCOVID-19-associated mucormycosis.[27-29]The Working Group on Zygomycosis of the European Confederation of Medical Mycology (ECMM) reported 17% mucormycosis cases from Europe, 18% from Italy, 23% from France, and 35%from Lebanon.[30]Recently, John *et al.* reviewed 41 cases of COVID-19-associated mucormycosis and identified the associated risk factors, clinical features, and outcomes. They reported that the co-infection was prevalent in 94% of patients with DM and presented as rhino-orbital and rhino-orbital-cerebral infections [31].

Hematologic malignancies and transplantation

Hematologic malignancies are a common risk factor for mucormycosis in developed countries such as the USA and Australia. The ECMM study reported HM as an underlying risk factor in 48% of patients with acute myeloid leukemia (AML). In contrast, 1 to 9% and3% cases of AML in Iranhave HM as the underlying risk factor [32]. According to the Transplant-Associated Infection Surveillance Network (TRANSNET) study conducted in the USA, the cumulative incidence was 0.29% for stem cell transplantation and 0.69% for mucormycosis [33]. Unlike HM and stem cell transplantation, solid organ transplantation is uncommon but an important risk factor for mucormycosis. The TRANSNET analysis revealed the cumulative incidence for solid organ transplantation as 0.07% and mucormycosis accounted for 2% of the cases [33]. The Prospective Antifungal Therapy Alliance (PATH Alliance) study reported that mucormycosis accounted for 1.6% of cases among 6,918 recipients [34].

Corticosteroids

Corticosteroids are frequently used to treat COVID-19 infections. However, their use in patients with DM tends to increase the risk of mucormycosis. The ECMM study revealed that 46% of patients had received corticosteroids and 44% had received other immunosuppressive agents before contracting mucormycosis [30]. Thus, steroids are considered as a major risk factor, especially in India that is struggling withtheCOVID-19 storm with secondary co-infections aggravating the situation.

Iron overload

Iron is an important risk factor involved in the pathogenesis of several diseases [35]. Under physiologic conditions, iron binds to transferrin and ferritinandits free form is unavailable.I n patients with DM, it's binding potential decreases, thereby increasing the susceptibility to disseminated mucormycosis [35].

Clinical forms of mucormycosis

Mucormycosis is clinically presented in six different forms based on its anatomic localization. Roden et al. reviewed and analyzed 929 cases of mucormycosis that occurred from1940 to 2003 [18]. Based on these cases, the most commonly reported sites of infection were found to be sinuses in 39% of cases, lungs in 24% of cases, and skin and soft tissues in 19% of cases. Disseminated infection was reported in 23% of cases [18].

Rhino-orbital-cerebral mucormycosis

Rhino-orbital-cerebral mucormycosisis the most common clinical presentation that usually occurs in patients with DM, renal transplants, neutropenic cancer, and organ transplant recipients (hematopoietic stem cell transplant or solid organ transplant) and other immunocompromised hosts [36]. The infection develops after the inhalation of fungal sporangiospores into the paranasal sinuses and may rapidly disseminate to adjacent tissues including orbits and the brain. Upon germination, the fungus invades the palate, sphenoid sinus, and cavernous sinus [1-4, 37]. The mold invades the cranium through the orbital apex or cribriform plate of the ethmoid bone. The symptoms of rhino-orbital-cerebral mucormycosis include headache, unilateral facial swelling, nasal or sinus congestion, serosanguinous nasal discharge, pain, and fever. In severe conditions, ptosis, proptosis, impaired extraocular muscle function, and vision impairment may occur [38]. The clinical diagnostic signs include necrotic black lesions on the hard palate or nasal turbinate and drainage of black pus from the eyes. A black necrotic eschar is the hallmark of mucormycosis [39]. A French study reported that 85% of rhino-orbital-cerebral cases were caused by *Rhizopus oryzae*, whereas only 17% of non-rhino cerebral cases were caused by *R.oryzae* [40].

Pulmonary mucormycosis

Pulmonary mucormycosis generally occurs in patients with HM or profound neutropenia. The clinical diagnosis of pulmonary mucormycosis is difficult due to the occurrence of non-specific symptoms such as fever, cough, chest pain, and dyspnea [41]. Invasion of pulmonary vessels may result in necrotizing pneumonia, pulmonary arterial aneurysms, and fatal aortic rupture [41, 42]. Reverse halo sign is the most common feature of pulmonary mucormycosis; it refers to a focus of central ground-glass opacities surrounded by a crescent or solid ring of consolidation [42]. The overall mortality with pulmonary mucormycosis ranges from 50 to 70%, which can increase to 90% in extrathoracic dissemination and 93.5% in mechanically ventilated patients in ICUs with invasive tracheobronchitis [41-43]. Acute Physiology and Chronic Health Evaluation (APACHE II) score, severe lymphopenia, and elevated serum lactate dehydrogenase levels are recognized as independent risk factors [44].

Cutaneous mucormycosis

Cutaneous mucormycosisis the third most common infection after rhino-orbital-cerebral and pulmonary mucormycosis. It usually occurs in children and immune compromised patients with a prevalence of 19% [45]. The lesions often progress to black eschars [45, 46].

Disseminated mucormycosis

Individuals who are at high risk of developing disseminated mucormycosis include neutropenic patients with pulmonary infection, patients with iron overload and profound immune suppression. It can spread hematogenously to the brain, spleen, heart, and other organs [47]. The high rate of dissemination explains the potential and predilection of mucorales in invading endothelial cells of the vascular system. The mortality rate of disseminated mucormycosis has been reported to be 96%. The early diagnostic hallmark of disseminated mucormycosis is metastatic skin lesions [47, 48].

Gastrointestinal mucormycosis

Gastrointestinal (GI) mucormycosisisthe less common clinical form that is known to occur in only 2 to 11% of mucormycosis cases [49]. However, the mortality rate of GI infections is 85%. It typically occurs in malnourished patients or premature infants. It affects the stomach, colon, and ileum due to the ingestion of contaminated food and is characterized by non/-specific symptoms such as abdominal pain, nausea, vomiting, and GI bleeding. Clinically, it resembles necrotizing enterocolitis in neonates, making the disease challenging to diagnose [50].

Uncommon mucormycosis

Other uncommon or unusual forms of mucormycosis include endocarditis, peritonitis, osteomyelitis, pyelonephritis, and catheter-related mucormycosis. The involvement of the brain without rhino-orbital presentation in intravenous drug abusers is the typical risk factor [51].

Among all these clinical presentations, rhino-orbital mucormycosis are commonly observed in patients with a history of DM and COVID-19. The prevalence data on clinical forms of mucormycosis associated with COVID-19 are unavailable. We have listed 10 recently published case reports and observational studies in Table 1 for a fair understanding of management of Covid-19 associated mucormycosis across the world.

Diagnosis and management

Early diagnosis and interventions including blood sugar control, removal of dead and necrotic tissue, and antifungal treatments, are significant in improving and controlling the disease outcomes. Diagnosis of mucormycosis includes recognition of risk factors and assessment of clinical manifestations by several methods based on microscopic evaluation, culturing and advanced molecular techniques [52].

Clinical assessment

Clinically, the diagnosis of mucormycosis is challenging due to the presence of non-specific symptoms. Tissue necrosis is the hallmark of mucormycosis; however, the absence of such features does not rule out the predisposition. More than 35 species under the class Mucormyceteshave different clinical manifestations, thus making the clinical assessment challenging.[53]A high index or algorithms are required to formulate for the diagnosis of such infections. For instance, Corzo-Leon et al. proposed "red flags/warning signs" algorithm for the diagnosis of rhino-orbito-cerebral mucormycosis in patients with DM that includes cranial nerve palsy, periorbital swelling, diplopia, sinus pain, proptosis,or a palatine ulcer.[54] The presence of any sign in a patient should immediately be assessed for mucormycosis using laboratory tests. The clinical assessment alone has low specificity and sensitivity. The classic diagnostic interpretation using imaging techniques such as radiography, computerized tomography (CT), and magnetic resonance imaging (MRI) may result in good clinical evaluation [52-55].

Laboratory tests

In clinical practice, laboratory testing of mucormycosis includes microscopic examination, histopathology, and culture examination. The histopathology examination of fungal hyphae in affected tissue biopsies or bronchoalveolar lavage (BAL) samples provides a definitive and confirmatory diagnosis of mucormycosis [56]. It reveals the presence of fungal infection and effectively distinguishes the contaminants. Staining methods including hematoxylin and eosin (H&E), Grocott's methenamine silver (GMS), and periodic acid-Schiff (PAS) staining can effectively show the structural degeneration, thus identifying the pathogen [57]. The members of ECMM and Mycoses Study Group Education and Research Consortium (ECMM/MSG ERC) have strongly recommended histopathology examination and direct microscopic evaluation of samples [30, 58].

Histopathologic and microscopic evaluation reveals the presence of the pathogen, whereas culture identifies the genus and species of the pathogen. Mucorales are generally thermos=tolerant that can grow as colonies at 37 ° C within 24 to 48 h and can be identified by matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry [59]. However, culture is less reliable due to a high risk of contamination and false-positive and false-negative results. False-negative culture results account for 50% of the cases in mucormycosis due to broken hyphae during sample processing [60]. Histopathologic examination along with culture is liable tool for the diagnosis of mucormycosis.

Molecular methods

Molecular methods are considered gold standards to confirm the infection and identify thespecies. Because theinternal transcribed spacer (ITS) region of fungal DNAis widely sequenced, ITS sequencing is a reliable and recommended first-line method for species identification.[61] Several polymerase chain reaction (PCR)-based techniques, including real-time PCR (RT-PCR), nested PCR alone or combined with restriction fragment length polymorphism (RFLP), and high-resolution melting (HRM) curve analysis, have been successfully used to detect the infection in the tissue or BAL samples [62, 63]. The molecular targets include 18S ribosomal RNA genes, 28S rDNA, the cytochrome b gene, and the Mucorales-specific *CotH* gene [62]. Non-invasive techniques to detect the infection include measuring monoclonal antibodies, 2DA6using sandwich enzyme-linked immunosorbent assay (ELISA), and lateral flow immunoassay (LFIA) in clinical samples [64]. These techniques have the potential to be used as a point-of-care test in clinical samples such as BAL, serum, and urine.

Management

Liposomal amphotericin B, a Food and Drug Administration (FDA)-approved agent, is the commonly used anti-fungal drug in mucormycosis cases. In severe cases, a combination of liposomal amphotericin B and posaconazoleis prescribed that exerts synergistic effects and inhibits hyphae formation [65]. Current guidelines in India recommend intravenous methylprednisolone. The National Institutes of Health (NIH) recommends the use of dexamethasone in patients on mechanical ventilation [66].

SUMMARY

In the present scenario, mucormycosis appears to be a result of an interaction of COVID-19 and poorly controlled DM. Although the cases of COVID-19-associated mucormycosis are well-documented, the exact number remains unclear. The epidemiology of mucormycosis is limited but evolving. Overall, the diagnosis of COVID-19-associated mucormycosis is a challenging task due to the lack of clinical suspicion and diagnostic facilities for the isolation of the causative fungus. Unfortunately, late diagnoses, limited access to the treatment, and the unproven impact of antifungal therapy have burdened the healthcare system. Rhino-orbital or rhino-cerebral presentations are commonly found in patients with a history of severe COVID-19 and DM [42, 67]. In such cases, utmost care should be taken for the diagnosis and management of the disease. Liposomal Amphotericin B is considered the drug of choice in most cases. Increased awareness, a high index of suspicion, better diagnostic facilities, and timely treatment are required to control these devastating infections.

Conflict of Interest: - None

Table 1: Recent cases of Covid-19-assoicated mucormycosis

References	Study type	Patient details	Symptoms	COVID-19-associated mucormycosis form	Interventions	Response status
Rao *et al.* [68]	Case report	A 66-year-old male with uncontrolled diabetes and use of systemic steroids for treating COVID-19	A sudden loss of vision in the left eye, with total ophthalmoplegia and diffuse opacification of the retina	Rhino-orbital cellulitis with ischemia of the orbital tissue	Endoscopic sinus surgery with orbital exenteration and intravenous liposomal amphotericin.	Recovered
Ravani et al. [69]	Retrospective, institutional cohort, interventional study	31 patients with a mean age of 56.3 years, uncontrolled diabetes (96.7%), and COVID-19 (61.2%), with concomitant steroid use in 61.2% of patients	Diminution of vision in 80.64% of patients and ophthalmoplegia in 77.4% of patients	Rhino-orbital mucormycosis	Intravenous liposomal amphotericin B and debridement of local necrotic tissue	Twenty-eight patients recovered and three patients died.
Arana et al. [70]	Case report	2 kidney transplant recipients with a history of type 2 DM and COVID-19	Mechanical ventilation and admission to the ICU	Rhino-orbital mucormycosis	Treatment with amphotericin B and an azole along with 6 subsequent ENT surgical debridement procedures	Recovered after 5 months
Krishna et al. [71]	Case report	2 cases in post-COVID-19 patients, who had uncontrolled type 2 diabetics	Swelling with pus discharge on the face	Maxillofacial infections	Intravenous liposomal Amphotericin B and surgical resection.	Recovered after 2 months
Maini et al.72	Case report	A 38-year-old male with COVID-19	Chemosis and pain in the left eye	Sino-orbital mucormycosis	Intravenous Fluconazole & Amphotericin B along with surgical debridement.	Recovered after 2 months with minimal residual deformity
Revannavar et al. [73]	Case report	A 38-year-old woman with diabetes and COVID-19	Left-sided facial pain, complete ptosis, and fever of short duration	Orbital apex syndrome with brain infarction	Conventional amphotericin B for 11 days.	Recovered.
Saldanha et al. [74]	Case report	A 32-year-old woman with uncontrolled diabetes	Left eye complete ptosis and left facial pain	Paranasal sinus mucormycosis	Endoscopic sinus surgery	Recovered after 2 months with reduction of facial pain and improvement in lagophthalmos but no improvement in vision.
Veisi et al. [75]	Case report	2 cases of COVID-19 under treatment with a corticosteroids	Vision loss, proptosis, orbital inflammation, and complete ophthalmoplegia	Rhino-orbital mucormycosis	Endoscopic sinus debridement and irrigation with diluted amphotericin B.	One patient survived and one died.
Sharma et al. [76]	Prospective observational study	33 patients with COVID-19, diabetes, and steroid therapy	Ethmoids	Paranasal sinus mucormycosis	Surgical debridement along with intravenous amphotericin	Recovered.

					administration.	
Johnson et al. [77]	Case report	A 79-year-old male with DM	Fever, rigors, dry cough, and worsening shortness of breath	Combined probable pulmonary aspergillosis and mucormycosis	Intravenous amphotericin administration.	Discharged to a long-term acute care facility.

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