

DIAGNOSIS AND TREATMENT OF MUCORMYCOSIS: AN INTRUDER POST-COVID-19

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ABSTRACT

Mucormycosis can be elaborated as mycosis due to *Mucorales*. Mucormycosis is an angioinvasive infection. Fungi of *Mucorales* order is the causative organism of mucormycosis and pertains to the class of zygomycetes. It is ordered on number third after candidiasis and aspergillosis in the category of invasive mycosis. *Rhizopus arrhizus* (oryzae) is the most important species which cause this disease. It is categorized as a disease with high mortality. There is a 46% chance of mucormycosis with person having sinus infection, 76% of chances with pulmonary infection, and 96% for disseminated Mucormycosis. The COVID-19 pandemic precipitated this disease in a common way. Around 90% of the population was exposed to coronavirus disease 2019 (COVID-19) infection during the pandemic which ultimately affected the immunity of individual, leading to increased chance of exposure to other infectious disease. Mucormycosis is one of such disease which can highly affect the individual with COVID-19 infection in patient's history. This review presents a brief about the disease origin, occurrences, types, signs and symptoms, risk factors, diagnosis, and treatments available, along with recent patents. This review also elaborated the treatment of COVID-19-associated mucormycosis and other risk factors. It was found that the diagnosis is not simple and easy sometimes it was observed postmortem also. This review also focuses on various methods with which easy diagnosis of this dreadful disease can be done.

Keywords: Coronavirus disease 2019 associated mucormycosis, European confederation of medical mycology, Patents, Epidemiology, and Therapy.

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INTRODUCTION

Saprobites originated from rotten matter or soils are the common causes of mucormycosis. It is a subtle fungal infection also known as zygomycosis as invented by American pathologist R.D. Baker. *Mucorales* and entomophthorales comprise zygomycetes and hence are a life-threatening invasive fungal disease [1-3]. This disease affects vital organs of the body such as the brain and can also cause internal damage to the ear, nose, throat, and mouth if not treated properly and strategically in 1876, Furbringer first reported few hundred cases of pulmonary mucormycosis in Germany [4,5]. Baker made a classic review of all the cases of, mucormycosis previously described in 1955. This review revealed that in the old German literature, there were six cases and ten cases in the American literature [6]. Mucormycosis shows symptoms such as one-sided facial swelling, headache, nose or sinus congestion, rapidly worsening black lesions on the bridge of the nose or upper mouth, and fever. The site of infection looks such as blisters and turns black due to which it is also known as "black fungus disease" [7].

The patients having previous history of infectious disease, that is, immunocompromised patients are at a great risk of mucormycosis [1-4]. The pancreatic beta cells are damaged due to diabetes resulting in least or no insulin production which leads to hyperglycemia condition [8-10]. This causes dysfunction of the immune response. The cases of diabetes mellitus (DM) are very high in India due to which the country stands in the second position for the highest number of DM patients in the population. DM has also been the most common underlying condition linked with mucormycosis in India [11]. The immune system of cancer patient weakens due to chemotherapy and radiations as they destroy cancer cells, which increase the chances of getting a fungal infection. Hence, cancerous patients are also at a high risk of mucormycosis. The patient with long-term use of corticosteroids with high blood glucose level can also be affected by mucormycosis. Organ transplant, stem cell transplant, Neutropenia (low number of white blood cells), and skin injuries due to surgery, burns, or wounds are also the conditions under which the patient is at high risk of mucormycosis [12].

The accelerating mode of coronavirus disease 2019 (COVID-19) pandemic is still on. Many countries including India have faced the second wave of this dreadful disease and some countries of the world have also suffered from the third wave which results in a panic situation. China has faced consecutive four waves of COVID-19 with maximum number of deaths [13]. As per the reports from Chinese Centre for Disease Control and Prevention on 25 December 2022, China's Zhejiang is facing millions new daily cases of COVID-19 infections. Use of antiviral drug like remdesivir and other supportive care equipments such as oxygen cylinders, ventilators, and heavy use of steroids was used in the management of COVID-19 as there was no specific drug discovered to treat the condition. In the middle of this pandemic, the COVID-19 patients are at a high risk of secondary infections such as mucormycosis also known as black fungus disease [14,15].

TYPES OF MUCORMYCOSIS

Rhino cerebral mucormycosis

It is also known as rhino-sinus mucormycosis. It covers a major portion of all types about 50%. The disease starts from palate necrosis, then orbit and intracranial structures are affected. The common symptoms under this type are fever, epistaxis, paralysis of face, obnubilation, etc. This type of mucormycosis is very fatal as it progresses to cavernous sinuses and cranial invasions, if not resolved initially. Furthermore, mortality rate is highest in this type, that is, about 35-70% [16].

Respiratory mucormycosis

Lung invasion is caused by spore's inhalation and it is the second most common clinical manifestation. Symptoms in this type appear in later stages. It includes necrotizing pneumonia and lung abscesses. It appears similar to invasive aspergillosis which dictates the presence of vascular invasion, thrombosis followed by tissue necrosis when investigated radiologically [17].

Cutaneous mucormycosis

Cutaneous mucormycosis can also be called as zygomycosis. This condition can develop on cutaneous and soft-tissues after burns, cuts, surgery, scratches, barrier ruptures, or after any kind of skin trauma.

The catheter insertion sites are also at high risk. Sometimes the intramuscular injections and contaminated dressings are also found responsible for the infection. "Hairy pus" in the form of cotton-like growth is the most significant symptom which is a representative of cutaneous mucormycosis. The mortality rate is low when diagnosed in early stages [18,19].

CNS mucormycosis

This type of Mucormycosis develops due to progression from rhino-orbital route. High mortality rate has found in case of delayed diagnosis.

Gastrointestinal mucormycosis

It is also another common type of mucormycosis. It can involve any part of digestive tract. The common signs and symptoms include abdominal pain and distention, along with nausea and vomiting. Rate of mortality is very high in this type [20].

THE UPSURGE IN MUCORMYCOSIS DUE TO COVID-19

Although it is a rare fungal disease, various underlying conditions such as sinus infection and pulmonary infection contribute to this fungal infection. COVID-19 enhances the risk of secondary infections as like mucormycosis because due to this infection, the patient is in immunosuppressed state. Various factors associated with COVID-19-infected patients during the second wave of pandemic attribute to mucormycosis fungal infection, also known as black fungus [21,22]. A 52-year-old woman from Hamirpur district of Himachal Pradesh was diagnosed with COVID-19-associated mucormycosis (CAM) in year 2021 after the second wave of COVID-19 pandemic. It was the first case of CAM reported in India. She was tested positive for COVID-19 on May 4, 2021, and also suffered from diabetes and high blood pressure. On May 28, 2021, 14,872 cases of mucormycosis were reported during the second wave of COVID-19 which was a drastic increment in the infection [7]. Gujarat with 3726 cases of mucormycosis was one of the states with highest number of cases of mucormycosis [23-26].

The former Health Minister Mr. Harsh Vardan announced that there were over 40,000 cases of mucormycosis in India. In May 2021, CAM was declared as epidemic and a notifiable disease in several states of India which included Rajasthan, Telangana, and Tamil Nadu, under the Epidemic Disease Act 1897. This disease is not contagious but can be life-threatening if not treated early [27-29].

The World Health Organization (WHO) also reported various cases of CAM in many countries such as Austria, Brazil, Egypt, France, India, Iran, Italy, and US. The Centre for Disease Control and Prevention, U.S., estimated the spreading rate of CAM as 0.14 cases/1000 people. This is around 80 times greater than in wealthy countries [29-31].

ETIOLOGY OF CAM

Lymphopenia due to COVID-19 causes considerable decrease in the number of T-cells (CD4+ and CD8+). T-cells play a key role in maintaining immunological memory and self-tolerance [32-34]. When the availability of T-cells is reduced due to COVID-19, it enhances the risk of fungal infection as like mucormycosis [35-37]. The other reason which contributes to the development of mucormycosis is the increased number of pro-inflammatory markers due to COVID-19 [38-40]. COVID-19 also caused marked deterioration of the lung tissue as it affected the pulmonary system to a great extent. It plays a supportive role for the development of mucormycosis and other disorders of respiratory system [41].

From the above discussion, it can be concluded that the etiology for CAM is related to various immune and inflammatory responses due to the coronavirus [42].

RISK FACTORS CONTRIBUTING TO CAM

The abrupt rise in the cases of mucormycosis in India during the COVID-19 pandemic seems to be multifactorial in nature. There are

various risk factors contributing to CAM which includes DM, long-term use of corticosteroids, antibiotics, and enhanced use of steam inhalation [18,43-45].

The use of contaminated or poor-quality oxygen cylinders, low-quality oxygen piping system, and ordinary tap water in ventilators are also some of the major risk factors. The sign and symptoms of CAM manifest during the recovery period of COVID-19.

Middle-aged patients of DM treated with steroids had a great risk of mucormycosis, when exposed to COVID-19 infection. Extensive review by Maertens et al revealed that 71.4% case of COVID-19 have received high dose of corticosteroids [55]. As per Indian authority recommendations during the initial period of pandemic, the patients with severe and critical COVID-19 were exposed to high methylprednisolone dose. The high dose of corticosteroids causes lymphopenia and T lymphocyte deregulation due to which the patients move to a more immunocompromised state and hence can be easily exposed to fungal attack as like mucormycosis [16,43,46-48]. A survey of COVID care center in India stated that 93% of the CAM patients had previous exposure to high-dose corticosteroids during the second wave of COVID-19. Use of home remedies during the COVID-19 pandemic had a strong emphasis on the population worldwide, among which one of them is steam inhalation. Intense steam inhalation causes mucosal erosion which can be a supportive environment for growth of fungal colonies of mucormycosis post-COVID-19. During the COVID-19 pandemic, the inappropriate use of broad-spectrum antibiotics especially macrolides causes the enhanced risk of CAM [49-52]. The broad-spectrum antibiotics cause hindrance in the healthy sinonasal microbiome and disrupt antimicrobial immune response. Azithromycin is also one of the antibiotics used for COVID-19 treatment which reduces the immune responses and promotes CAM. COVID-19 second wave broadly affected the lungs of the patients and caused pneumonia due to which insufficient oxygen in the body leads to the death of the patient [53]. The COVID-19 pandemic in 2021 accelerated the demand of the oxygen globally to such level that some countries were unable to fulfill high oxygen demand. As per the WHO reports, 20-40% of death due to COVID-19 pandemic were due to scarcity of oxygen supply under medical facilities. This medical emergency required high oxygen production [54]. The chances of addition of impurities and contamination increase to many folds due to its high demand. Low-quality oxygen cylinders and piping system promoted the growth of CAM. The black fungus travel to the nasal tract which subsequently grown in the nostril moving toward eyes and then brain which resulted in the paralysis of nerve and permanent damage to the eye. It could also result in heart attack [30]. Other than these, excessive use of zinc supplement and no or improper use of mask during COVID-19 or post-COVID-19 are also some risk factors which were responsible for causing CAM [55].

MANAGEMENT OF CAM AS PER EUROPEAN CONFEDERATION OF MEDICAL MYCOLOGY (ECMM)

CAM cases were grown unexpectedly after the second wave of COVID-19. The management of mucormycosis associated with COVID-19 was a challenging task for the clinicians [55].

The collaborated efforts of ECMM and the International Society of Human and Animal Mycology (ICHAM) issued guidelines for the management of CAM in public interest. This resulted in removal of the false conception about the diagnosis and treatment of the diseases. The recommendations served by ECMM and ICHAM helped the clinicians to manage the infection [56].

Diagnosis

As per ECMM guidelines, two methods for diagnosis of CAM include imaging and mycological diagnosis. This includes Magnetic Resonance imaging (MRI) and Computed Tomography (CT) imaging study of brain and paranasal sinuses for precise diagnosis [57-60]. MRI should be

Table 1: Patents related to mucormycosis

Claim	Patent No.	Inventor	Description
Use of coth for immunotherapy and diagnosis of mucormycosis	US20190194301A1 United state	Ibrahim AS, Liu M, Ghebremariam T, Fu Y, Edwards JE, Filler S.	This invention describes the composition and method for targeting specific protein or nucleic acid of fungi that causes mucormycosis [71].
Procedure for diagnosing and monitoring mucormycosis	EP2646829A1 Europe	Luppi M, Barozzi P, Potenza L, Vallerini D, Forghieri F.	This invention describes the procedure with which diagnosis and monitoring of mucormycosis can be done. In this, the biological fluid of the patient is exposed to mucor antigen and then the <i>Mucorales</i> -specific T cells are identified by various <i>in vitro</i> detection methods. These methods are immunoenzymatic assays (ELISPOT, Quantiferon) or of immunocytofluorimetric assay [Cytokine Secretion Assay (CSA), Intracellular Cytokine Staining (ICS)] [72].
Treatment method for mucormycosis and other epiphyte diseases	CN101511360A China	Ibrahim AS, Spielberg BJ, Edwards JE.	This invention provides a composition of at least a iron chelating agent and one antifungal agent with which mucormycosis or other epiphyte disease can be treated effectively [73].
Composition of vaccine for mucormycosis	CN102639557A China	Ibrahim A.S., Spielberg B.J., Edwards J.E.	This innovation involves description of vaccine developed for treatment and prevention of various fungal diseases including mucormycosis [74].
Use of the combination of iron chelator and antifungal agent for the treatment of mucormycosis	NZ 574862A New Zealand	Ibrahim AS, Spellberg BJ, Edwards JE.	The efficient treatment of various infectious diseases specially fungal disease as like mucormycosis can be done by this invention. [75].
Mucormycosis treatment agent	JP2021134176A Japan	Chibana H, Chika H, Chibana H.	This invention involves isolation of an antibiotic siccamin which is isolated from <i>Helminthosporium siccamin</i> Drechsler culture filtrate that can be a safe and effective therapeutic agent for treatment of mucormycosis [76].
Approach for prevention and treatment of mucormycosis	US20210284742A1 United state	Bruno V, Watkins TN, Ibrahim A.	This invention provides an approach for prevention and treatment of mucormycosis. In this approach, a therapeutically effective amount of agent is administered which is capable of suppressing a signaling pathway of a receptor which is selected from the group which constitutes epidermal growth factor receptor, platelet derived growth factor receptor, ErbB2/Her2, progesterone receptor and a combination thereof [77].
Method of preparation of feed for treating mucormycosis of <i>Cyclospora trifasciata</i>	CN104872438A China	Dongxiu S, Jingjia C.	This invention discloses a preparation method of a feed for treating mucormycosis of <i>Cyclospora trifasciata</i> by resisting bacterium, diminishing inflammation, enhancing the immunologic function of the body which can lead to reduce death rate [78].
Tools and methods for diagnosing/testing mucormycosis	JP6742611B2 Japan	Takeya H, Kaneko Y, Miyazaki Y, Yamagoe S.	This invention reveals a diagnostic method for diagnosing mucormycosis by detecting a protein specific to <i>Rhizopus</i> which can only be found in the biological sample of an individual infected with mucormycosis [79].
Compositions and methods for the treatment of mucormycosis and other fungal diseases	BRPI0714221A2 Brazil	Spellberg BJ, Edwards JE, Ibrahim AS.	This invention reveals the tools and methods for diagnosing and testing mucormycosis [80].

preferred over CT scan as MRI helps in diagnosing the extend of fungal infection and CT scan diagnoses the bony erosion which is observed only at the later stage of the infection [61].

In mycological diagnosis, the samples are taken from the abrasions due to mucormycosis. The sample can be bronchoalveolar lavage (BAL) sample, mini-BAL non-bronchoscopic lavage, and trans-bronchial biopsy from pulmonary mucormycosis. The histopathological and/or microbiological examination of the sample is done [62-64].

Treatment

Treatment of CAM is similar to the treatment for mucormycosis patients without COVID-19 history. The aggressive growth of the disease should be controlled first by eliminating predisposing factors such as diabetes and ketoacidosis.

When the condition is not treated within 6 days, the mortality rate can be increased to folds. Hence, the treatment of the disease should

be done with underlying formulations as soon as the diagnosis is done [57]. The first-line treatment of CAM can be done by anti-fungal agents amongst which Amphotericin B is the most effective anti-fungal drug. Isavuconazole and posaconazole injections can also be used if the patient is intolerant to polyene. Itraconazole is also an alternative drug for treating CAM, if the previously discussed drugs are unavailable or unsuitable for the patient [58]. The local control of the affected area due to CAM can be done by surgical endoscopy of the affected internal tissues and bones during the progression of the disease. This results in higher survival rate of the CAM-infected individuals. The disease can be recurrent due to some remains of infection left in the operated area. Repeated debridement can be done in such cases [59-65].

Prevention

ECMM also issued preventive measures to avoid the exposure of COVID-19 patients to mucormycosis. During the treatment for COVID-19, strict control on glycemic level is required [66-68].

Use of systemic corticosteroids should be used only in emergency condition as like hypoxia, along with the maintenance of glycemic level. Steroid therapy should be under limited dose. Surgical or three-layered linen mask should be used, so that exposure to the fungal infection is reduced. General awareness to the recovered patients of COVID-19 should be given by the health officials regarding the signs and symptoms of CAM. This includes facial pain, nasal blockage, excessive discharge, loosening of teeth, chest pain, and respiratory insufficiency [69,70].

PATENTS RELATED TO MUCORMYCOSIS

There are some of the patents published till now related to the mucormycosis as depicted in Table 1. There is a lot of scope of discovery in the field of CAM. The patents related to CAM are under process and have a future scope of patent publication and grant.

CONCLUSION

From the above review, it can be concluded that mucormycosis is a dreadful disease which can affect a large number of the population having previous history of COVID-19. Various patents have also been filed related to the treatment and diagnosis of CAM which is not published yet. Hence, an urgent attention is required to aware the patients with high risk of mucormycosis to control the growth of this epidemic in urban as well as rural areas. Developing rapid laboratory diagnostic methods, specific vaccines and therapies for the prevention and treatment of CAM should be a part of the effort to limit the outbreak. At present, no specific anti-mucormycotic drug is available for effective and targeted treatment of this disease. Hence, this compiled information can be helpful to the researchers working in the field of diagnosing and treating CAM. The majority of the population is affected with COVID-19 pandemic once or twice during this pandemic, so cumulating the share of risk of mucormycosis to such COVID-19 patient and its treatment can be of great discussion which can be clarified by this review. The development of vaccine for this pandemic can also be a major outbreak for controlling the spread of this pandemic.

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DK: Depth revision of article and approved version for publication. SM: Developing the concept and design of the article. BV: Have reviewed the work for maintaining the integrity of the article. KV: Data collection from different sources. SB: Drafted the article including accession of data.

CONFLICTS OF INTEREST

There were not any potential conflicts of interest between the authors.

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