Original Article

A Brief Review About Mucormycosis (Black Fungus)

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Abstract

In this article, we will talk briefly about mucormycosis (Black Fungus). Mucormycosis is a name that most doctors are acquainted with, and it refers to a collection of different mycoses caused by one of the several saprophytic fungi in the Mucorales order. Although the number of Mucorales species that cause human disease is small, case reports imply that, under the right circumstances, species of Mucorales that were previously thought to be harmless commensals could produce invasive disease. The fact that the names of the fungi have changed over time as more information about their taxonomy has been revealed has made identifying organisms recovered from human infections more difficult. To add to the confusion, mucormycosis has been given several other names, none of which are particularly helpful from a medical standpoint. Mucormycosis was referred to as phycomycosis while Phycomyces was part of the taxonomic lexicon. Mucorales-related disorders have also been given the label Zygomycosis. The name zygomycosis refers to the Zygomycetes class, which includes both Mucorales and Entomophthorales, which cause diseases that are fundamentally distinct from those caused by Mucorales. Furthermore, the name of mycotic diseases is not usually taken from the name of the causative fungus class. As a result, mucormycosis and entomophthoramycosis appear to be appropriate nomenclature for the two diseases caused by the Mucorales and Entomophthorales, respectively. The goal of this study is to go over the most up-to-date information on mucormycosis.

Key Words: Mucormycosis, Epidemiology, Risk Factors, Causes, Treatment.

INTRODUCTION

The name "mucormycosis" refers to a group of illnesses caused by fungi in the Mucorales order of the Zygomycetes class that can be chronic, subacute, or fast progressive. Mucormycosis has a wide range of clinical manifestations, including sinusitis (pansinusitis, rhino-orbital, or rhino-cerebral), pulmonary, cutaneous, gastrointestinal, disseminated, and other unusual manifestations. Rhizopus spp., Mucor spp., Rhizomucor, and Leichtheimia spp. are the most prevalent agents that cause mucormycosis. Cunninghamella, Saksenaea, and Apophysomyces are some of the less usually implicated taxa in infection. These organisms can be found in a variety of places in nature, including decomposing organic substrates and soil. **[1] [2] [3] [4]** Mucormycosis is known to affect immunocompromised patients, who are frequently neutropenic, as well as those with uncontrolled diabetes and ketoacidosis. Mucormycosis is known to affect immunocompromised patients, who are frequently neutropenic, as well as those with uncontrolled diabetes and ketoacidosis. Other risk factors include iron overload, for example, is a danger factor.

Clinical characteristics largely depend on the organ involved and are most usually associated with the paranasal sinuses and lungs, and to a smaller extent, the gastrointestinal tract. **[5]**

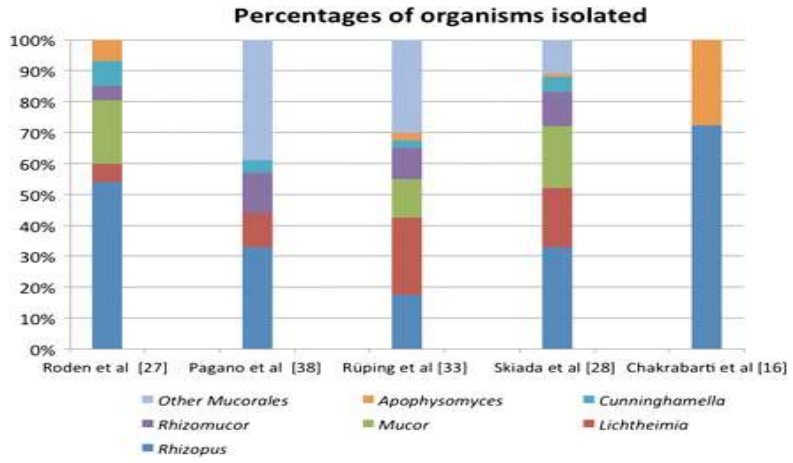

Figure no 1 Arendrup MC et al 2015

Risk Factors

Diabetes as a danger signal between the developed and developing worlds, there are considerable differences in the risk factors for mucormycosis. While Hematological cancers and organ transplants are listed as the main risk factors for mucormycosis in affluent countries, the condition is primarily linked to uncontrolled diabetes in developing nations like India, whether or not the patient has ketoacidosis. The majority of mucormycosis cases reported from India, between 24 to 64 percent, occur in people with uncontrolled diabetes, whether or not they have ketoacidosis. Although other risk factors have also been identified, their significance is overshadowed by the vast majority of mucormycosis cases associated with uncontrolled diabetes. This may be due to the previously mentioned high prevalence of diabetes in these nations. These patients postpone seeking medical care unless a problem arises in India, between 16 and 23 percent of diabetics have an undiscovered underlying condition when mucormycosis first manifests; in these circumstances, the mucormycosis serves as a diagnostic marker for diabetes. Before developing mucormycosis, the mean informed length of diabetes was determined to be 2–10 years. **[9] [10]**

Poorly managed type II diabetes is the most frequent risk factor for mucormycosis among diabetic patients; it accounts for about 44–88% of cases, mostly in northern to southern India, and over half of them show ketoacidosis. Some patients have also been found to have type I diabetes (10–15%) and secondary diabetes. Diabetes was a risk factor in only 36% of the 929 cases in the global series, 17% in the trans-European series, 16% in the French series, 6% in the Belgian series, and 18% in the Italian series. However, it should be highlighted that people with diabetes in India have also been shown to have renal failure and chronic liver disease linked to alcoholism. **[11] [12]**

Causes

Mucorales are thermotolerant saprophytic fungi that can be discovered in soil samples and decomposing organic materials. According to an ecological study on Mucorales in Indian soils, pathogenic species such Rhizopus, Lichtheimia, Cunninghamella, Rhizomucor, and Apophysomyces were isolated. Similar to this, an Indian study using aeromycological analysis in a hospital and community environment revealed the identification of pathogenic Mucorales in air samples. Mucorales' taxonomy is changing; mucormycosis has been linked to 11 different genera and 27 different species. **(7)(8)**

Causative agents of mucormycosis in India.

^ Causative Agents	Chakrabarti et al., 2001; 2006; 2009 [14–16]	Manesh et al., 2019 [17]	Chander et. al., 2018 [22]	Prakash et al., 2019 [5]	Patel et al., 2020 [6]	Priya et al., 2020 [18]
Total number of isolated Mucorales	120 $	184	60	239	290	25
Rhizopus species	79 (65.8) [a]	143 (77.7)	28 (46.7)	193 (80.8)	231 (79.7)	14 (56)
Rhizopus arrhizus	74 (61.7) [a]	91 (49.5)	17 (28.3)	124 (51.9)	176 (60.7)	-
Rhizopus microsporus	4 (4.2) [b]	32 (17.4)	9 (15)	30 (12.6)	32 (11)	-
Rhizopus homothallicus	1 (3.1) [c]	-	2 (3.3)	6 (2.5)	22 (7.6)	-
Apophysomyces species	31 (25.8) [a]	20 (10.9)	13 (21.7)	22 (9.2)	23 (7.9)	5 (20)
Lichtheimia species	3 (5.3) [d]	1 (0.5)	8 (13.3)	10 (4.2)	10 (3.5)	1 (4)
Saksenaea species	3 (3.4) [e]	1 (0.5)	5 (8.3)	2 (0.8)	2 (0.7)	-
Cunninghamella species	-	1 (0.5)	-	5 (2.1)	3 (1)	-
Mucor species	1 (4) [f]	4 (2.2)	1 (1.7)	3 (1.3)	16 (5.5)	3 (12)
Rhizomucor species	2 (2.3) [g]	1 (0.5)	1 (1.7)	-	4 (1.4)	-
Syncephalastrum species	1 (3.1) [c]	1 (0.5)	4 (6.7)	-	1 (0.4)	-
Nonsporulating Mucorales/other fungi	-	12 (6.5)	-	4 (1.7)	-	2 (8)

Figure no 2 Sipsas NV et al 2018

The Rise of Mucormycosis in Covid-19 Patient in India

The wave 2 Covid-19 pandemic's attack has proven too much for India's healthcare system to handle. Over 400,000 cases of Covid-19 were being recorded daily at their height in early May 2021 **[15],** and India was caught off guard with a severe lack of medications, vaccines, ventilators, and oxygen **[16].** Although Covid instances are currently under control,

mucormycosis, sometimes known as "black fungus," is an uncommon but seriously dangerous fungal infection that is currently causing a public health disaster in India. Rhizopus and Mucor are the most prevalent species in the group of moulds known as mucormycetes, which are the source of mucormycosis **[17].** According to Mr. Harsh Vardhan, the former health minister of India, as of June 28, 2021, there have been over 40,000 cases of mucormycosis documented. **[18] .**Mucormycosis has been labeled an epidemic and a disease that needs to be reported in numerous Indian states. Early detection and timely treatment beginning are essential because the disorder can progress quickly and have a catastrophic outcome. Antifungal drugs are used in conjunction with rigorous surgical debridement of necrotic tissue, if necessary, to treat this illness. Liposomal Amphotericin B at a dose of 5 mg/kg/day is the suggested anti-fungal medication. The severe lack of Amphotericin B and its high cost to patients and their families, on the other hand, pose significant challenges. There are various theories associating severe Covid-19 patients who are immune compromised and/or have concomitant comorbidities to mucormycosis, suggesting that the etiology of the abrupt rise in mucormycosis in India is multifaceted in nature. For instance, it has been discovered that diabetes, a known risk factor for Covid, is also substantially linked to the risk of mucormycosis. Around 1.5 million fatalities worldwide were related to diabetes, and its incidence is rising quickly in low- and middle-income nations, according to the WHO **[19].** The prevalence of diabetes is rapidly increasing in India, which is home to approximately 77 million diabetics and has the second-highest number of diabetics worldwide **[20]** behind China. and that diabetes is becoming more and more common in India. **[21]** Nearly 80% of the 100 or so Covid subjects with mucormycosis in recent research also had diabetes **[22].** The surge in mucormycosis in individuals with a history of Covid has been linked by medical and public health experts to the indiscriminate use of steroids and other broad-spectrum antibiotics. For instance, if used impulsively, steroids, which can save lives when taken wisely, could end up injuring the patient utilized since they elevate blood sugar levels and are known to lower immunity, both of which increase the chance of acquiring mucormycosis **[23].** Additionally, specialists link the spread of mucormycosis to the current dominant SARS infection variations, specifically the Delta form observed in India **[24].** However, it should be highlighted that no conclusive evidence linking the dominant Delta variation to mucormycosis has been found. Additionally, the use of additional unproven Covid treatment plans, such as zinc and iron supplements, which help the fungus thrive by creating the ideal environment, is also connected to the increase. Others have linked the increased prevalence of mucormycosis to the unsanitary usage of masks, as well as prolonged use of ventilators and humidifiers. The use of industrial oxygen cylinders for medicinal purposes as a potential relation to an increase in mucormycosis among Covid patients, however, is a theory that has gone unreported by the international medical community but is being disputed by some professionals in India **[25,26].** It should be mentioned that the Indian state of Karnataka recently permitted a team of microbiologists to investigate the connection between mucormycosis cases and the usage of industrial oxygen in Covid patients **[27].**

PATHOGENESIS

Mucorales spores cause a significant inflammatory reaction in healthy hosts when inhaled or injected. Spores must avoid being destroyed by local mononuclear and polymorphonuclear phagocytes to germinate into hyphae, which are the angioinvasive form of the infection and eventually spread to other organs, to establish infection.**[28]** Consequently, illnesses linked to compromised or inadequate immune systems are the most prevalent underlying predisposing conditions for mucormycosis. Phagocyte activity, such as extended or Patients with significant neutropenia were HM, taking excessive doses of corticosteroids, having poorly managed type 2 diabetes, and/or without iron overload or diabetic ketoacidosis. Infection is generally preceded in individuals who are not seriously impaired by injury (infection of the skin and sensitive tissues), illegal intravenous drug usage, and newborn preterm in the case of gastrointestinal mucormycosis or malnutrition.**[28]**

Although little is known about the crucial virulence factors in Mucorales, the information that is now available suggests that a number of the fungus's characteristics contribute to its rapid growth in patients. These elements consist of: the ability of these fungi to grow quickly and alter their cell walls to endure harsh circumstances; their natural thermotolerance **[29]**; some species' capacity to bind to proteins that control glucose on endothelial cell surfaces**[30]**; and the capacity of certain Mucorales to produce iron permeases, which release sequestered free iron, or heme oxygenase, which removes iron from host hemoglobin**[31].**

The distinct sensitivity of iron-overloaded individuals confirms the significance of iron acquisition in the development of mucormycosis. This invasive fungal infection has hosts. Patients with transfusional/dyserythropoietic iron excess are disproportionately susceptible to acquiring widespread manifestations of this unusual infection.**[32]**; Similar to this, individuals with diabetic ketoacidosis (pH 7.3-6.8) have elevated serum levels of free iron, which promote the growth of Mucorales like R. oryzae.**[33][34]**, due to the transferrin's reduced ability to connect to molecules at acidic pH.

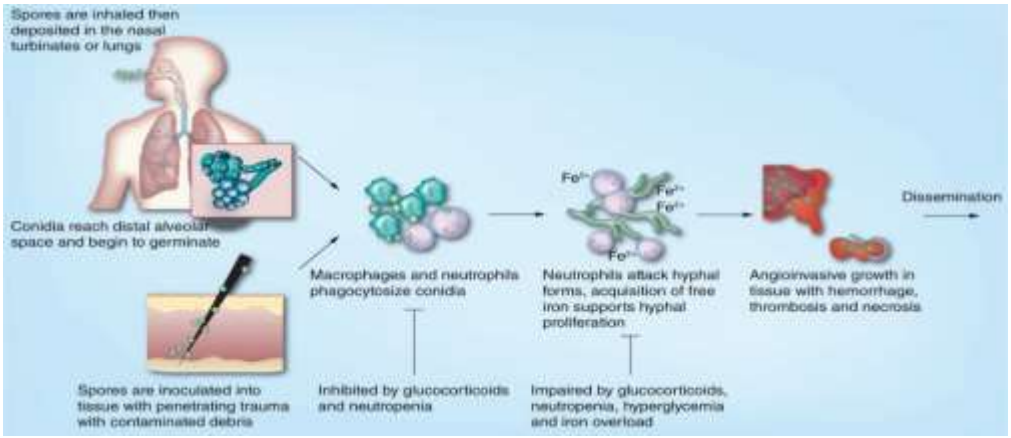

Figure no 03 Orne C, et al 2018

Diagnosis

Diagnostic methods that take a clinical approach have poor sensitivity and specificity. The absence of a necrotic eschar does not rule out the diagnosis of mucormycosis, which is characterized by tissue necrosis brought on by angioinvasion and thrombosis. Although mucormycosis may be the cause of necrotic cutaneous lesions in immunocompromised patients, additional infections such as Aspergillus, Fusarium Pseudallescheria, and Scedosporium species are also on the differential diagnosis list.**[44]** For an early/quick diagnosis of mucormycosis, lateral flow immunoassays (LFIA) and enzyme-linked immunoassays (ELISA) are being developed. A thorough analysis of a monoclonal antibody (2DA6) that reacts with isolated mannans of diverse fungi was conducted. The Zygomycota and Ascomycota fungi both contain the conserved -1,6-linked mannose, which is recognized by the 2DA6 antibody. In this study, it was shown that LFIA was more practical than ELISA and that it could be utilized as a point-of-care test.**[45]** Employing bronchoscopic alveolar lavage fluid (BAL), serum, urine, and tissue, LFIA using a monoclonal antibody 2DA6 directed to cell wall fucomannan of mucormycosis was assessed as a diagnostic test in a murine model of invasive mucormycosis. The test was quick, early (within 3-4 days of infection), and accurate in identifying R. delemar, L. corymbifera, M. circinelloides, and C. bertholletiae**. [46]** There is currently no FDA-approved serologic test for invasive mucormycosis diagnosis. There is however, optimism that in the future, tests like LFIA employing mannan unique to the problematic fungus may be made available. The LFIA's main advantages are its simplicity of use in clinics and speedy diagnosis. However, there is always the worry that the target (like Mannan's) may impact the test's sensitivity due to the target's variation between species.**[45]** There is now considerable study into the use of PCR testing for the early diagnosis of Mucorales in high-risk patients. Cerebrospinal fluid, or CSF, has been analyzed in a few isolated cases **[47, 48],** and tissue has been tested using a variety of molecular targets. These tests have shown promise in the evaluation of PCR for the diagnosis of Mucorales. IHC, in addition to pcr, might increase the precision of the histopathological diagnosis of mucormycosis, even if the majority of studies are somewhat small, employ various reagents and methodologies, and are susceptible to publishing and selection biases. In limited research by Jung J, et al, the test has 100% sensitivity and 100% specificity in 7 confirmed instances of mucormycosis. Twenty (87%) of 23 possible invasive mould infections had mucormycosis IHC results that were positive. However, a few specimens of IHC failed to stain and several tested positive for both Aspergillus and Mucorales, suggesting that there may be cross-reactivity **[49]**. IHC has been demonstrated to identify to the genus level (Rhizomucor spp.) however, it has been primarily successful for Mucorales as a class. IHC has been demonstrated to identify to the genus level (Rhizomucor spp.) despite Mucorales as a class being largely successful **[50].**In conclusion, even though IHC may not be as sensitive as PCR-based testing, it might be crucial in identifying the many fungal genera. Matrix-assisted laser desorption ionization-time of flight mass spectrometry is another promising diagnostic culture-based method to identify Mucormycetes (MALDI-TOF MS).

Identification is based on study of the protein composition of the treated or undamaged cells of the unknown microbe using species-specific spectra, which are regarded as the protein fingerprint of a microorganism when compared to reference spectra in a database **[51,52].** The optimal mass spectral identification method for moulds should be quick and easy to use, resilient against changes in culture conditions, reproducible, and applicable to the majority of microorganisms. It should also be cost-effective **[53].** The subject of fungal diagnostics is rapidly developing, with a focus on Mucorales in particular.

Even though PCR, in particular, shows a lot of promise for detecting mucormycosis early on and has higher sensitivity and specificity than typical microbiologic techniques, there are still several problems that need to be worked out. Their widespread acceptance has been limited by the variety of platforms available, variations in PCR primers and probes, and a lack of standardization of these tests.

Mixed fungal infections are prevalent but can be overlooked **[54,55].** Reagents used to process tissue that are infected with fungus DNA can cause false positive tests. The damage to fungal DNA caused by formalin treatment can make it more difficult to identify specific species **[56].** Another issue is the lack of publicly accessible, validated fungal genome libraries for PCR, as well as the frequent misidentification of sequences due to the libraries' fast updates with new species **[57,58].** Having said that, we believe that molecular diagnostic tests will be crucial in identifying Mucorales to the genus

and species level in the future when fungal invasion is noted on tissue samples (with negative microbiologic cultures) or to the species level when the fungus is isolated from routine culture. The method also shows potential for monitoring treatment response and screening for very early illness in high-risk patients.

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