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MUCORMYCOSIS – A REVIEW ON PATHOGENESIS, CLINICAL TYPES AND MANAGEMENT.

M. Aswin Monisha*	CRRI, Karpaga Vinayaga Institute of Dental Sciences, Chengalpattu. *Corresponding Author
A Banu Jothi	CRRI, Karpaga Vinayaga Institute of Dental Sciences, Chengalpattu.
Dr. L. P. Raghupathy	Senior Lecturer, Department of Oral Medicine and Radiology, Karpaga Vinayaga Institute of Dental Sciences, Chengalpattu.
Dr. K.R. Shakila	Professor, Department of Oral Medicine and Radiology, Karpaga Vinayaga Institute of Dental Sciences, Chengalpattu.

ABSTRACT Mucormycosis is a rare invasive fungal disease responsible for significant morbidity and mortality in immunocompromised patients, especially those with haematological malignancies, hematopoietic stem cell transplant recipients, and patients who undergo chronic high-dose corticosteroid treatment. It is an Angio invasive fungal infection caused by fungus belonging to the order Mucorales. Recently, it was discovered that COVID-19 and mucormycosis are inextricably linked. A causative link between COVID-19 and mucormycosis has yet to be shown, glucocorticoids, deteriorating blood glucose management, and viral-induced lymphopenia have all been implicated in the development of mucormycosis in COVID-19 patients. Diagnosis of mucormycosis is challenging and relies on a combination of a suggestive clinical picture, predisposing factors, compatible radiological findings, and histopathological and/or microbiological evidence of Mucorales which is highly dependent on the available techniques and trained personnel. The present review focuses on the brief summary of mucormycosis, its pathogenesis, clinical types and symptoms and its management.

KEYWORDS : Mucormycosis, Fungal infections, Fungal diseases, COVID – 19, Corticosteroids

INTRODUCTION

Mucormycosis is an Angio invasive fungal infection caused by fungus belonging to the order Mucorales. The disease was first described in 1876 by Fürbinger, Germany in a cancer patient whose right lung showed a haemorrhagic infarct with fungal hyphae and a few sporangia [1]. The fungal infection mucormycosis, also known as zygomycosis, is caused by moulds named mucormycetes. Fungi can be found in a variety of environments, including soil, manure, rotting plants, and leaves [5]. Zygomycetes is derived from the Greek word "zygos" for balance. The majority of Zygomycetes reproduce clonally (asexually) by producing nonmotile (aplanosporic) mitospores ranging in size from 3 to 11 m. They are formed in many or few spored sporocarps (sporangia and sporangiola/merosporangia, respectively) and are soil-, air-, feed-, and food-borne. Whittaker initially referred to the Zygomycetes as the "Phylum des Zygomycetes" (phylum Zygomycota) [3]. Mucormycosis comes in a variety of types, including disseminated, rhino cerebral, pulmonary, cutaneous, and renal mucormycosis. Fungal infections are more common in people on steroids, diabetics, immunocompromised patients, patients with haematological malignancies, and solid organ transplant recipients. Recently, it was discovered that COVID-19 and mucormycosis are inextricably linked [5]. The newly discovered coronavirus (SARS-CoV-2) pandemic is still doing havoc in numerous countries of the world, including India [2]. Although a causative link between COVID-19 and mucormycosis has yet to be shown, glucocorticoids, deteriorating blood glucose management, and viral-induced lymphopenia have all been implicated in the development of mucormycosis in COVID-19 patients [4].

Epidemiology:

The annual incidence of mucormycosis in India rose from 12.9 cases in the years 1990–1999 to 89 cases in the years 2013–2015. In southern India alone, the number of cases was 18.4 per year in the years 2005–2015. The estimated prevalence of mucormycosis in India is 70 times higher than the global prevalence, which is 0.02–9.5 cases per 1,000,000 people [5]. Immunocompromised patients, in particular those suffering from the repercussions of uncontrolled diabetes, bone marrow or solid organ transplantation, corticosteroid medication, haematological malignancy, and trauma, are more vulnerable to the infection. Mucormycosis mortality and morbidity rates vary depending on the organ affected by the infection, the causative fungal species, and the patient's medical status; for example, sinus infections resulted in 46% mortality, while pulmonary and disseminated mucormycosis infections resulted in 76% and 96% mortality, respectively. Patients receiving stem cell and solid organ transplantation have a greater chance of survival, as evidenced by mortality rates of 8% and 2%, respectively [3].

Causative Agent:

Inhalation, ingestion, or direct inoculation allow fungus spores to enter the human body. Rhizopus arrhizus (formerly Rhizopus oryzae) is the most prevalent species worldwide [1]. A recent study of soil samples from different geographical areas in France discovered Rhizopus arrhizus (synonym: Rhizopus oryzae), Mucor circinelloides, Lichtheimiacorymbifera, Rhizopus microsporus, and Cunninghamella bertholletiae to be the most infectious via inhalation or ingestion of contaminated food, even though detection in nasal mucus is hampered by mucociliary transport-mediated removal. Mucoralean fungi are feared for causing lethal disease in a broader variety of human and animal hosts than other opportunistic fungi if the predisposing risk conditions become favourable for infection [3].

Predisposing Factor:

Mucormycosis can cause the following diseases: (1) rhinocerebral mucormycosis, which can infect the sinuses and the brain, causing fever, swelling of one side of the facial organ, black lesions inside or outside the mouth, headache, and sinus congestion; (2) pulmonary mucormycosis, which mainly infects the lung, causing chest pain, breathing disturbance, fever, and cough; and (3) cutaneous mucormycosis, which causes local skin infections like ulcers,redness and swelling; (4) gastrointestinal mucormycosis, which is uncommon in adults but more common in premature neonates and causes nausea, vomiting, gastrointestinal bleeding, and abdominal pain; (5) disseminated mucormycosis, which occurs in patients with multiple medical complications, making symptomatic

differentiation of mucormycosis from other infectious diseases difficult; and (6) unusual presentation as renal infection [3].

The fungal culture specimens showed the presence of Aspergillus flavus, Candida glabrata, and Candida albicans. Aspergillus and Candida are the most common fungal infections identified in COVID19 patients. Mucor and Cryptococcus are the other uncommon fungi that affect the lungs in COVID19 patients. Yang et al. reported that the mortality among 52 critically ill patients out of 710 patients admitted at the Wuhan Jin Yintan hospital from December 2019 to January 26, 2020, with SARS 2 was higher compared to the SARS and Middle East respiratory syndrome infections. In 5% of the 52 critically ill patients, fungal coinfections such as Aspergillus flavus, fumigatus, and Candida albicans were found. The reason for the fungal infections in COVID19 is due to lymphopenia and immune-mediated changes. There is an abnormality in the number of granulocytes and monocytes; COVID19 also damages the lung tissues and makes them more susceptible to fungal infections. A study that compiled case report data from 41 COVID19 associated mucormycosis patients discovered that 94% of them had diabetes. An alteration of iron metabolism occurs in the COVID19 infection. Diabetic ketoacidosis may induce ferritin synthesis and increase the intracellular concentration of iron. The autopsies performed on the COVID19 patients showed vascular endothelial injury and new vessel formation [5].

Chronic administration of corticosteroids and other immunosuppressive agents is an important risk factor for mucormycosis. They are used in the treatment of malignancies, transplantation, and autoimmune diseases. Corticosteroids impair migration, ingestion, and phagolysosome fusion in macrophages. In addition, they may lead to drug-induced diabetes. Mucormycosis is a risk factor for prolonged (>3 weeks) high-dose systemic corticosteroids. However, there have been reports of mucormycosis associated with short courses of corticosteroids. Other diseases associated with mucormycosis are intravenous drug use, AIDS, renal failure, liver diseases, chronic alcoholism, malnutrition, and low birth weight infants [9]. Mucormycosis in patients who are HIV-positive is extremely rare [1].

Clinical Manifestation

Mucormycosis infection in humans is classified into two types: superficial and visceral infection and localised and disseminated infection. The external ear, fingernails, and skin all exhibit the superficial form. Visceral forms manifest as pulmonary, gastrointestinal, and rhinocerebral types. Entry of these spores may take place either through the cutaneous or respiratory routes [7].

Rhino Cerebral

Mucorales infects the head and neck region in well-defined stages. Infection begins in the palate or the paranasal sinuses, progresses to the orbit, and, if not diagnosed early, to the brain. For simplicity, the term "rhino-orbito-cerebral mucormycosis" will be used to refer to any stage of this type of infection [8]. Its clinical manifestation starts with palatal and sinus necrosis and further enters the orbit prior to affecting intracranial structures [7]. Signs and symptoms can include fever, lethargy, headache, orbital pain, abrupt loss of vision, ophthalmoplegia, proptosis, ptosis, a dilated pupil, corneal anaesthesia and clouding, chemosis, periorbital cellulitis, sinusitis, epistaxis, facial palsy, trigeminal nerve distribution sensory loss, and seizures [8]. Malignancy, diabetes, and organ transplant are underlying risk factors. The mortality rate is 50% or may be higher depending on the concentration of immunosuppression [6].

PULMONARY

This is the second most common site of Mucorales infection involvement. Inhalation of spores is the primary route of infection. Mucorales can produce an asymptomatic mycetoma, similar to Aspergillus. Hypersensitivity pneumonitis to Rhizopus has been reported in Scandinavian sawmill workers (so-called woodtrimmer's disease) and in farm workers [8]. In this case, hyphae invaded the pulmonary blood vessel, resulting in hemorrhage, ischemia, thrombosis, and distal tissue infarction. Symptoms like prolonged fever, non-productive cough, and endobronchial lesions result in obstruction of the airway and haemoptysis [6]. Patients with leukaemia have traditionally been considered to represent the majority of cases; however, recent papers have suggested diabetes mellitus to be the most prevalent underlying condition. Tedder et al. reviewed 255 cases of mucormycosis that involved at least the lungs; 39% had an underlying haematological malignancy, 32% had diabetes mellitus, 8% had undergone organ transplantation, and 18% had renal failure [8]. Its mortality rate is 66% or higher, depending on the level of immunosuppression [6].

Gastrointestinal

Gastrointestinal mucormycosis has rarely occurred after renal, liver, and heart transplantation. One third of the cases of gastrointestinal mucormycosis occur in infants and children. In children less than 1 year of age, the stomach (59%) and colon (53%) have been the most commonly involved sites, followed by the small bowel (24%). In children aged 2–18 years, the stomach has been involved in 85% of cases, the oesophagus in 38% of cases, the small bowel in 31% of cases, and the colon in 31% of cases. Malnutrition has been present in 50% of cases [8]. It occurs by ingestion of contaminated milk, porridge, bread, alcoholic drinks, herbal, and homoeopathic formulations, due to which the stomach and colon get affected [6].

Cutaneous

Due to direct spore inoculation into the skin, which can lead to widespread illness, however the chances of this occurring from an internal organ to the skin are quite rare. In susceptible hosts, skin damage or burns are underlying risk factors. Symptoms appear Gangrene and hematogenous spread can occur if the disease progresses gradually to invasive, fulminant disease. It has a 25% mortality rate, which varies with disease severity [6].

Diagnosis:

Clinical diagnosis has a limited sensitivity and specificity. Mucormycosis is distinguished by tissue necrosis caused by angioinvasion and thrombosis; nevertheless, the absence of a necrotic eschar does not rule out the diagnosis. Mucormycosis may cause necrotic cutaneous lesions in immuno compromised patients, however other infections such as Aspergillus, Fusarium, Pseudallescheria, and Scedosporium species should be considered. The existence of mucormycosis in a susceptible host is suggested by a history of voriconazole prophylaxis or the appearance of breakthrough fungal infection while receiving medicines efficacious against Aspergillus but not Mucorales. Imaging investigations are useful in differentiating invasive fungal infections [1]. According to Kontoyiannis et al., one of the greatest challenges in identifying mucormycosis is its indefinable clinical presentation and repeated occult distribution, necessitating the use of a sensitive, nonculture-based investigative method [7]. Higher-resolution computed tomography (CT) and magnetic resonance imaging (MRI) can be highly useful in diagnosing pulmonary, rhino-orbital-cerebral, and disseminated mucormycosis. A "halo sign," defined as a ground glass opacity surrounding a lung nodule on CT images of pulmonary mucormycosis, was seen in 78% of the nodules. When compared to other lung fungal infections, CT images revealed a reverse halo sign, i.e., a ring of consolidation surrounding a centre of ground glass opacity,

which is an excellent predictor of pulmonary mucormycosis [6].

Lab Investigation:

In clinical practice, laboratory diagnosis of mucormycosis includes histopathology, direct examination of wet mounts, and culture. [1]

Microbiological Investigations

Mucorales are saprophytes that can be found in soil and decaying organic waste. They grow in a wide range of temperatures, 25-55 °C, on most routine bacterial (e.g., sheep blood agar, chocolate agar) and fungal culture media (e.g., Sabouraud dextrose agar, inhibitory mould agar, potato dextrose agar). Mucorales in clinical specimens grow at 37°C, forming fluffy white, grey, or brownish colonies that quickly fill the Petri dish within 1-7 days. Mechanical homogenization of tissue specimens can reduce culture output [8].

Non-invasive Investigations

Most of the above-mentioned techniques require invasive procedures, which may not be appropriate for specific patient groups (hematologic malignancies with thrombocytopenia, ICU patients, etc.). Despite the infection's Angio invasive nature, blood cultures remain negative. In reality, just a few instances with positive blood cultures have been reported thus far. Fungal DNA, on the other hand, circulates in the blood. As a result, there is a lot of active research concentrating on non-invasive approaches for detecting circulating mucoralean DNA in blood (plasma or serum) or urine, such as qPCR [1].

Treatment

Successful treatment of mucormycosis requires rapid correct diagnosis, surgical debridement, and medication administration, as well as supplementary application of hyperbaric oxygen, recombinant cytokines, or transfusion of granulocytes and a prosthetic obturator [42, 46]. According to Spellberg et al., currently available monotherapy has a high death rate, particularly in haematology patients, and so "combination therapy" for mucormycosis is preferred. The key to controlling mucormycosis is early detection. Treatment success is mostly dependent on early and accurate diagnosis, as well as prevention of predisposing factors linked with mucormycosis [6]. AmB dexycholate, liposomal AmB (5-10 mg/kg), AmB lipid complex, AmB colloidal dispersion, Posaconazole (400 mg daily), and care of core disorders are all antifungal medications. Caspofungin and lipid AmB or lipid AmB and Posaconazole are second-line treatment alternatives; grouping with Deferasirox is not indicated. Diabetics may have a better prognosis than nondiabetics. Yohai et al. reported an overall survival rate of 77% in diabetics and 34% in non-diabetics for rhino orbito-cerebral mucormycosis. Blitzer et al. found a similar survival rate of 60% in diabetics and 20% in non-diabetics in patients with rhino-orbito-cerebral mucormycosis [8].

Prevention And Care

Primary care level

- Look for the warning signs and symptoms of mucormycosis.
- Consider mucormycosis in cases of blocked nose or sinusitis in immunocompromised patients and/or COVID19 patients.
- Blood sugar monitoring in patients with COVID19 and diabetes mellitus; steroid therapy Taper steroids in postCOVID-19 patients on long-term steroid therapy
- Refer to a specialist for further investigation (potassium hydroxide staining and culture).

For mucormycosis management,

- Do appropriate investigations as early as possible, such as KOH staining and microscopy, culture, and MALDI-TOF, for the detection of fungal infection [5].

CONCLUSIONS

The epidemiology of mucormycosis is evolving. In light of new evidence, diabetes mellitus remains themain underlying disease globally. As diabetes rates are rising, especially in low- and middle-income countries, a rise in mucormycosis cases is expected, and this should be alarming [1].

COVID-19 and COVID-19-associated) is exceedingly common in India and has mostly gone unnoticed for decades. More research is needed to determine the pathophysiologic basis of CAM, particularly the influence of SARS-CoV-2 on host innate immunity and interactions with various Mucorales species. [2] Diabetes is the most common risk factor for COVID-19-associated mucormycosis, followed by steroid use and contaminated oxygen [5]. Mucormycosis is a rare invasive fungal invasion that primarily affects diabetics, immuno compromised people, and those receiving iron overload treatment. It was recently discovered in the bodies of SARS-CoV-2-infected individuals with a greater fatality rate. It was discovered that, due to a severe scarcity of sterile oxygen, a quick supply of industrial oxygen was delivered to rescue the patient, allowing microorganisms of mucormycosis to infiltrate the immunocompromised patients, who also suffered from black fungus [6].

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