| Review | Article |

Mucormycosis or black fungus: An emerging threat in COVID-19

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Article Info

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Introduction

Coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome virus 2 (SARS-CoV-2), has affected more than 160 million people worldwide, accounting for over 3.4 million deaths on the day of 23rd May 2021.[1] In addition to that, mucormycosis infection, a rare fungal infection, commonly known as the 'black fungus', are emerging as a matter of concern in COVID-19, especially in the Indian sub-continent. In India, around 9000 cases of deadly mucormycosis have been reported, and it has become a growing epidemic of the disease.[2] On 25th May, two cases of mucormycosis have been declared in Bangladesh.[3] Mucormycosis is not a new disease; the incidence rate of this disease has increased over the last decade, mostly seen among patients with hematological malignancies and recipients of allogeneic hematopoietic stem cell transplantation. In the present COVID-19 situation, the incidence of mucormycosis is changing among diabetic populations, most commonly in developing countries or patients with limited access to medical care for diabetes.[4] It is possible that the irrational use of steroid is one of the critical factors for mucormycosis to be increasingly prevalent in COVID-19.[7]

Epidemiology

Mucormycosis is a relatively uncommon but life-threatening severe fungal infection caused by a group of molds called mucormycetes.[5] It is saprophytic nonseptate or sparsely septate fungi of the order Mucorales.[6] It causes angio-invasion and associated with high morbidity and mortality.[7,8] Mucormycosis is previously known as 'zygomycosis'. After the proposed elimination of the phylum Zygomycota, fungus associated with mucormycosis now taxonomically reclassified under the phylum Glomeromycotan. Therefore, taxonomically or clinically, 'mucormycosis' is a more appropriate term than 'zygomycosis' for these infections.[4,9]

Humans get this infection mostly by inhalation of sporangiospores and occasionally by ingestion of food contaminated by the fungus or traumatic inoculation. Morphologically the funguses under Mucorales are broad, aseptate or sparsely septate ribbon-like hyphae, and it is ubiquitous. The most common etiological agent is *Rhizopus arrhizus*. Infections due to *Rhizopus microsporus*, *Apophysomyces variabilis*, and *Rhizopus homothallicus* are increasing. Some rare agents are *Saksenaea erythrospora, Mucor irregularis, and Thamnostylum lucknowense*.[10-13]

There is a difference in the prevalence of mucormycosis between the western world and Asian countries.[13] Due to the low sensitivity of diagnostic tests and difficulties in collecting test sample from deep tissue, the true incidence/prevalence of mucormycosis is challenging to estimate. According to the Leading International Fungal Education (LIFE) estimation, a portal that measures the global burden of serious fungal infections, the annual prevalence of the disease might be around 10,000 cases globally except India. If India is included, the number will be 910,000 cases globally.[6,14] The exact incidence of mucormycosis in India is unknown due to the lack of population-based study.[6] Bangladesh has no data regarding the prevalence or incidence of mucormycosis at present.

Risk Factors

There are several risk factors and underlining diseases responsible for mucormycosis. Diabetes mellitus with or without complications, e.g., Diabetic ketoacidosis (DKA), is the leading among the underlying risk factors for mucoromycete infection.

Haematological malignancies (especially acute myeloid leukaemia) and solid-organ transplants are also prevalent as risk factors after DM.[6,13] The most common risk factor for Asian and African countries is diabetes mellitus, whereas for western countries (including Europe, the United States, Australia and New Zealand), haematological malignancies and transplantation are the major risk factors.[13,15,16] Another important risk factor is corticosteroid therapy, and probably the irrational use of steroid is one of the critical factors for mucormycosis to be increasingly prevalent in COVID-19.[7] Other risk factors are chronic kidney disease (CKD), pulmonary tuberculosis and chronic obstructive pulmonary disease (COPD).[12,17] Major/minor trauma is another important risk factor in mucormycosis cases and many patients present with cutaneous mucormycosis after trauma, burns. Iatrogenic trauma at the surgery or injection site, contaminated intramuscular injections, adhesive tapes and endo-bronchial tubes were sources of infection in nosocomial mucormycosis.[18,19] Intravenous drug use, autoimmune disease, HIV infection, immunosuppressant drugs, malnutrition, and ICU stay are also risk factors.[6]

Types

According to anatomical site involvement, the most common type of mucormycosis is rhino-orbito-cerebral or rhinocerebral. This type of infection starts after inhalation of fungal sporangiospores into the paranasal sinuses and migrates to the brain through either the orbital apex or cribriform plate of the ethmoid bone. This form is mainly seen among people with uncontrolled diabetes and people who have had a kidney transplant. The second most common form is pulmonary (lung) mucormycosis and is often associated with hematological disorders and transplant recipients. Other clinical forms are gastrointestinal, cutaneous, renal, disseminated, and uncommon rare form where infection occurs in bones, heart, ear, parotid gland, uterus, urinary bladder and lymph nodes.[12,13,20-22]

Pathogenesis

Due to the ubiquitous in nature, Mucorales are commonly available in the environment around us. People with immunocompromised state such as with poorly controlled or uncontrolled diabetes mellitus (especially with ketoacidosis), on glucocorticid treatment , neutropenia in hematologic or solid malignancy, have undergone transplantation, have iron overload, and who have suffered from burns are at high risk of having the disease with the pathogen.[23]

Inhalation of conidia, ingestion with foods and traumatic inoculation of the pathogen are the common routes of infection. According to the site of deposition of the spore, disease manifestation occurs, for instance, when spores are deposited in the turbinate of the nasal cavity, the rhino-cerebral disease develops; when inhaled, the pulmonary disease develops; when ingested, GI disease

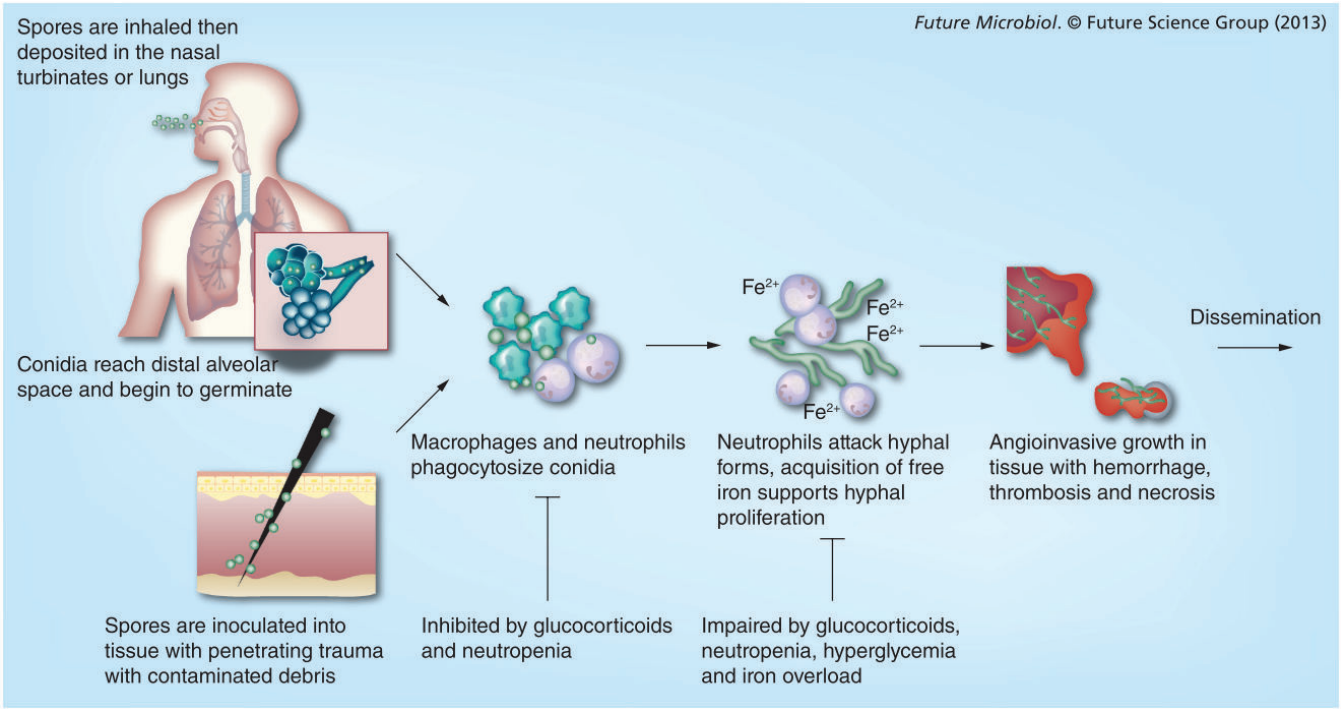

Figure: Pathogenies of mucormycosis.[4]

ensues; and when the agents are introduced through breached skin, the cutaneous disease develops.[23]

When the molds of mucormycosis get into the tissues from the environment, it turns into hyphal forms. Fungal hyphae invade blood vessels and produce tissue infarction, necrosis, and thrombosis. Neutrophil comes into the field as the primary host defence, and as a result, neutropenia or neutrophil dysfunction occurs. For this reason, individuals with neutropenia or neutrophil dysfunction (e.g., diabetes, steroid use) are at the highest risk.[23]

Pathogenesis of increased risk of mucormycosis in COVID-19 pandemic

It is found in the recent past that mucormycosis is occurring frequently in COVID-19 patients. The main reason postulated to be increase germinations of Mucorales in COVID-19 patients. The germination is occurring due to several reasons such as low oxygen saturation, high blood sugar level in COVID-19 due to pre-existing diabetes, new onset hyperglycemia, steroid induced hyperglycemia, metabolic acidosis, high iron level as evidenced by high ferritin, immunosuppression due to SARS-CoV-2 mediated, steroid mediated or pre-existing comorbidities causing decreased phagocytic activities by white blood cells. There are other risk factors like prolonged hospitalization and increased ventilator use in COVID-19 might have contributed in increased risk of mucormycosis.[24] Use of industrial oxigen and use of contaminated masks are also though to be risk factors for this conditions.[24]

Clinical Feature

Tissue necrosis due to angioinvasion and subsequent thrombosis the key or hallmark feature of invasive mucormycosis. Based on the site of invasion, clinical symptoms vary in the different form of the disease. One-sided facial swelling, headache, nasal or sinus congestion, black lesions on nasal bridge or upper inside of mouth and fever are the common symptoms in Rhinocerebral type. Whereas cough, chest pain, shortness of breath, along with fever seen in pulmonary mycosis. Gastrointestinal mucormycosis may present with abdominal pain, nausea, vomiting and gastrointestinal bleeding. Blisters or ulcers along with blackening infected area usually seen in mucormycosis in the skin. The skin lesion may be painful, swelled, warm and reddish.[4,24]

Diagnosis

The key points for the diagnosis of mucormycosis infection comprise of high index of suspicion, underlining risk factors, and assessment of clinical manifestation.[25] Most often, the clinical features and radiographic manifestations of mucormycosis are inconclusive and non-specific.

A complete blood cell (CBC) count can be done to assess for neutropenia. Moreover, blood glucose, bicarbonate, and electrolytes are helpful to monitor homeostasis and direct correction of acidosis. An arterial blood gas (ABG) study can help determine the acidosis and guide corrective therapy. Evidence of iron overload can be assed by high ferritin levels and a low total iron-binding capacity. In cerebrospinal fluid (CSF), elevated protein levels and a modest mononuclear pleocytosis can be seen in cases of central nervous system (CNS) involvement.[28,29]

Blood cultures can be obtained; however, they are usually negative despite the angioinvasive nature of the organism. Blood cultures may be helpful to detect bacteremia in addition to Mucorales infection.

As this infection shows rarely positive in blood culture, direct examination of sputum, broncho alveolar lavage fluid or paranasal sinus secretions should be consider as the most rapid approach for a first orientation of diagnosis.[25,26] Direct microscopy of clinical specimen preferably using optical brighteners such as Blankophor and Calcofluor White is also considered as a rapid presumptive diagnosis of mucormycosis.[27] Moreover, the culture of specimens is an essential investigation, though only one-third of microscopically positive specimens shows positive specimen culture.[28,29]

Histopathological examination cannot differentiate between *Aspergillus* or morphologically related fungi and Mucorales. However, this distinction is significant to initiate life-saving therapeutic interventions. In many cases, mixed infections may occur, and a proper diagnosis is necessary, either by culture or molecular-based assays.[30] Identification of mucomycocyte species can be done for better epidemiological knowledge and interest. There are some serological investigations including enzyme linked immunosorbent assays, immunoblots and immunodiffusion tests; and molecular assays including conventional polymerase chain reaction (PCR), restriction fragment length poly-morphism analyses (RFLP), DNA sequencing of defined gene regions, and melt curve analysis of PCR for detection or identification of Mucorales are also useful to aid the diagnosis.[25,31]

Treatment

According to the guidelines from the 3rd European Conference on Infections in Leukemia, the four cornerstones for management are 1) early recognition or rapid diagnosis, 2) rapid initiation of effective antifungal therapy, 3) appropriate and extensive surgical debridement of infected tissue (especially in rhino-cerebral or skin infections), and 4) controlling predisposing factors and underlying disease (rapid reversal where possible).[24.32,33]

Early diagnosis is probably the most influencing factors for the survival of the patient. Any delay in initiating antifungal therapy provides more time for fungus to invade through deeper tissue and blood vessel and consequently spread into vital organs.[34]

In antifungal therapy, the most effective available drugs are amphotericin B (and the lipid formulations), posaconazole, or isavuconazole. Amphotericin B, posaconazole, isavuconazole can be administered in IV route whereas posaconazole and isavuconazole available for both IV and oral route. Commonly used antifungal drugs, including fluconazole, voriconazole, and echinocandins, are not seen to be effective against fungi that cause mucormycosis.[4,35] As delaying in starting treatment is associated with increased mortality, it is important to start one of these antifungals as soon as possible. Amphotericin B is often used as the first-line treatment.[33,34,36] IV use of posaconazole is more beneficial than oral preparation due to increased bioavailability for patients with underlying renal dysfunction who may not tolerate a lipid amphotericin B formulation.[4] A new triazole, isavuconazole, has a modest effect on Mucorales in vitro, thus in future, as an alternative, it may be a potential drug for some susceptible strains.[37]

Immediate surgical resection of lesions is recommended for any patient with isolated cutaneous or sinus disease for the aggressive nature of the infection. In aggressive sinus disease, radical debridement, including enucleation of the eye, maybe required.[4,32,33] In some retrospective case series, better survival has been seen where patients received surgical debridement in conjunction with systemic antifungal therapy.[38-41]

Adjunctive therapies for mucormycosis include iron chelation, hyperbaric oxygen, cytokine therapy and some other drugs. However, due to lack of available data for iron chelation, not widely available for the hyperbaric oxygen role of these adjunctive therapies is under active investigation.[24]

Prognosis

The overall prognosis of mucormycosis infection depends on several factors, including the rapid diagnosis and treatment, the site of infection, underlying conditions and the immune status of the patient.[28] But, timely diagnosis is important, otherwise it may cause increased morbidity and mortality of the patient in COVID-19 pandemic. Therefore, physician needs to be vigilant regarding suspecting the cases and start treatment as early as possible.

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