Mucormycosis (Black Fungus)

1Dr. Puja Bansal, 2Sunayani Panda, 3Sunidhi Sangam, 4Shashwat Prasad

1Professor, 2,3,4Student
School of Dental Sciences, Sharda University,
Greater Noida, U.P., India

Abstract: Mucormycosis or black fungus infection is a rare but deadly disease with a 46–96% mortality rate depending on the underlying health condition of patients. This life-threatening new enemy has challenged the Indian healthcare system during the massive second wave of covid-19 pandemic. Recently, the covid patients in India are getting infected by this uncommon fungus at higher rates than ever. At present, the prevalence of this black fungus infection is skyrocketing among covid-19 and post-covid-19 patients in India. As of June 8, 2021, India recorded 28,252 mucormycosis cases. Among them, 86.0% had a history of covid19.

Introduction
Mucormycosis is also termed as black fungus due to the necrosis of affected tissue of patient's skin which turns it into black. “Mucormycosis” is the rarest type of fungal infection in order of importance after candidiasis and aspergillosis. It caused by Mucormycetes belong to the class Zygomycetes having order Mucorales. The mucormycetes mould mainly occurs in soil, leaves, decayed wood, manure etc. Species of Mucoraceae family i.e Rhizopus arrhizus, Rhizopus pusillus, Apophysomyces elegans, Absidia elegans and Mucor racemosus are most common cause of the disease [1,2,3,4,5].

This infection mainly targets diabetic and immune-compromised patients. As COVID-19 infection declines the immunity of patients, so mucormycosis cases are also increasing due to inhalation of molds containing industrial oxygen [6]. Mucormycosis – An opportunistic infection in the aged immunocompromised individual [7].

Pathophysiology
Sporangiospore ingestion or inhalation or inoculation of spores via wounds or trauma, inhalation of saturated oxygen, medical equipment or improper ventilation system are the ways through which black fungus got inside of a patient [8,9,10]. Phagocytes play an important role in infection of Mucorales. The hyphae and spores of molds which cause mucormycosis can be easily countered by mononuclear or polymorphonuclear phagocytes. Therefore, persons with very low number of phagocytes or impaired phagocytosis function are at greater risk of black fungus infections [11]. Excessive chemotherapy can lead to development of neutropenia which become a soft target for this mucormycosis. Along with this, patient with defective neutrophil function due to poor controlled of blood glucose level, acidic pH and ketoacidosis hyperglycemia can severely damage motility and phagocytic capacity of neutrophil [12]. Moreover, phagocytic function can also be compromised by over-dose of glucocorticoids due to which they will not be able to kill the ingested Mucorales [13]. The metabolism of iron plays a significant role in pathogenesis of mucormycosis. Mucormycosis have the capacity to extract iron from host for their survival and multiplication as well as to perform various enzymatic activities. Rhizopus oryzae was used for evaluating iron sequester activity and it was found that, mucormycosis grow rapidly in iron containing media but very poor growth in serum devoid of iron [14]. Mucormycosis have a specific mechanism to invade the endothelial cells from vascular system due to which infection got disseminated from one to other parts of the body. During glucose starvation, GRP78 receptors on cell surface got upregulated and acts as receptors for Mucorales in human for destroy the endothelial cells [15].

Clinical manifestation
Mucormycetes mould can invade in the susceptible host via nostrils, mouth or burned/disrupted skin which results in rhino-orbito-cerebral, gastrointestinal or cutaneous wound infections[16]. Mucormycosis also results in vascular thrombus and may lead to tissue necrosis [17].

Patients with uncontrolled diabetes and leukemia: Studies suggested that Rhino cerebral Mucormycosis is most common among all other cases of Mucormycosis. Sometimes progression of rhino-cerebral Mucormycosis may leads to central nervous system and it becomes fatal. The second most preferred site of infection could be lungs and sinuses. Mortality rate associated with lungs infection may be over 60% [18].

In severe Covid-19 situation patient: It could develop dysfunction of immune system with decrease in lymphocyte counts and exponentially rise in inflammatory cytokines such as IL-6, IL-1β, IFN- γ, MCP-1, IP-10, IL-4, IL-10 and Tumor necrosis factor (TNF) that leads to hyperinflammation in the lungs and some patients may leads to death[19,20].

Patients with solid organ or bone marrow transplant, liver cirrhosis, neutropenia are also more susceptible to get infected with Mucormycosis. As these patients have lesser number of monocytes and neutrophils which has ability to inhibit mucormycetes mould[21].

Chelation therapy with DFO and Iron overload: In dialysis patients to treat iron and aluminum overload, use of iron chelator and DFO therapy can produce higher risk for angioinvasive mucormycosis. McNab AA et al. said that according to a report of an international registry, 78% of dialysis patients who received DFO had mucormycosis. Disseminated mucormycosis is most common in case of patients receiving DFO treatment with 80% mortality rate [22].
Black fungal infection/mucormycosis in association with COVID-19

One of the newer problems arising recently in India and also in some other countries is black fungal infection or mucormycosis in COVID-19 as well as post COVID-19 patients. Mucormycosis is mainly arising in COVID-19 patients due to the use of steroids as a medication to suppress highly active immune system, so that it can help COVID-19 patients to protect their lung from damage by a mechanism known as “cytokine storm”. Based on the recent scenario of increasing cases of mucormycosis in COVID-19 patients, the physician should keep eyes on their patients even after complete recovery from this disease [23,24]. By observing the early symptoms of mucormycosis i.e. fever, swelling of one side of the face, black discharge from nasal, pain in head, blockage of nose, teeth weakness, appearance of black patches on nose and upper inner side of the mouth, blurred and weak vision, brain infection, ulceration inside the mouth, breathlessness, pain in chest and redness and loss of sensation in cheeks area in COVID-19 patients physician can identify the infection and give early treatment to prevent the spread of disease to other organs as well as to cure this infection at early stage to decrease mortality rate [25,26].

Signs and symptoms

During treatment or post Covid-19 patient's complaint for fever, headache, and reddish swollen skin over nose and around eyes all are the major signs and symptoms of Mucormycosis [27]. Patients also reported visual abnormalities, eye swelling, ocular pain, facial edema and breathe shortening. Diabetic patients also reported for the symptoms of diplopia which is also the sign of infection[18]. In scientific terminology sinus pain, proptosis, periorbital swelling, orbital apex syndrome and ulcer of the palate and cranial nerve palsy are the major symptoms of Mucormycosis infection[28].

Diagnosis

Diagnosis of mucormycosis is a challenging task but based upon identification of characteristic symptoms, detailed patient history, thorough clinical evaluation and specialized tests dedicated physician can diagnose it. Mucormycosis doesn't respond to any antigen detection test as galactomannan antigen test is available for detection of aspergillosis[4]. Direct microscopy (wet mounts method) of infected tissue using fluorescent brighteners i.e. Blankophor, Calcofluor white with potassium hydroxide is also used for rapid diagnosis and visualization of characteristic fungal hyphae. Culture of specimen is also important method as mucorales are able to grow rapidly at temperature of 24–37 °C within a time frame of 24–48 h. Tissue culture method allows identification to the level of genus and species[29].

Black Fungus Treatment

Mucormycosis treatment must be fast and aggressive. The concern is due to the fact that by the time even a presumptive diagnosis is made, the patient has often suffered significant tissue damage which cannot be reversed. Most patients will need surgical and medical treatment. Most infectious disease experts say that without aggressive surgical debridement of the infected area, the patient is likely to die. Medicines play an important role. Two main aims are sought simultaneously: antifungal drugs to slow or stop the fungal spread and drugs to treat debilitating underlying diseases. Amphotericin B (initially intravenous) is the usual drug of choice for antifungal therapy.

Posaconazole or isavuconazole can treat mucormycosis. Patients may even require an intravenous antifungal procedure lasting 4 –6 weeks. Patients with underlying diseases like diabetes need to be in optimal control of their diabetes. Patients normally on steroids or taking deferexamine (Desferal; used to remove excess iron from the body) are likely to have these drugs stopped because they can increase the survival of fungi in the body. Patients may need additional surgeries and usually need antifungal treatment for an extended period (weeks to months) depending on the severity of the disease[30].

Conclusion

COVID-19 causes sustained lymphopenia being reported in 85% of cases. So, there is decrease in number of T cells, CD4 cells and CD8 cells. This decreased count of T cells makes a person prone to fungal co-infections. COVID-19 also cause excessive lung damage and alveo-interstitial pathology. It makes a favourable chance of fungal infection. Some experts plead that use of industrial oxygen over medical oxygen may be the culprit of fungal infection. Due to the sudden rise of cases and decrease supply of medical oxygen, hospitals were diverted to use of industrial oxygen. Medical oxygen is highly purified. Before being used, it undergoes different processes such as compression, filtration and purification. Its cylinders are cleaned and disinfected also. But these criteria are not fulfilled by industrial oxygen. So, use of uncleamed industrial oxygen may be a probable cause of the black fungus surge. Mucormycosis should always be taken into consideration when a patient at risk presents with unilateral facial swelling, proptosis, facial pain or swelling. Diagnosis is based on combination of clinical symptoms, radiological findings, histopathological examinations and microbiological culture. Radiology is helpful for determination of extent of disease. A combined approach is followed for treatment. Patients with mucormycosis are undergone with exenteration of affected part and administration of intravenous liposomal amphotericin B (5-10 mg/kg/day) along with blood sugar control. It is utmost important to initiate treatment as the earliest because a delay of 6 days may lead to doubling of mortality.

References


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