

Black Fungus And Covid-19 Disease In Diabetes Mellitus Patients

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Abstract- After first phase of Covid-19, the second wave affects a lot to the Indians with mysterious fungal infection known as Mucormycosis. Here, we reviewed clinical pathogenesis, signs, symptoms and treatment against black fungus. The conclusion revealed that use of immunosuppressant to combat Covid-19 also increases the risk to get infected with mucormycosis. Patients with hyperglycemia, ketoacidosis, solid organ or bone marrow transplantation, liver cirrhosis, neutropenia are more susceptible to get attacked by Mucormycosis moulds. Early diagnosis, removal of predisposing factors, timely antifungal therapy with surgical removal of all infected tissues and adjunctive therapies are four major factors to eradicate Mucormycosis.

Keywords- covid-19, mucormycosis, black fungus, hyperglycemia, Immunosuppressant

I. INTRODUCTION

India affects a lot with the worldwide pandemic Covid-19 caused by “Severe acute respiratory syndrome Corona virus-2 (SARS-CoV-2)”.¹ First case of COVID-19 was reported in Kerala, India on 30th January 2020, afterwards highest cases i.e. 1 lakhs per day were reported for the year by May 2020.² After mid June recovery of patient's increases successively with decrease in infection rate, further active case dropped to less than 15000 in January 2021. Afterwards second wave was begun in March 2021 with a larger blow of active cases than first wave with deficiency of hospital beds, vaccines, medicines, oxygen cylinders and oxygen. The daily reported cases were reached to around 4.5 lakhs in starting of May 2021.³ The effect of Covid-19 ranges from mild to moderate to life threatening with some associated disorders such as diabetes mellitus, cardiac diseases and immune compromised conditions.^{4,5} Research articles also reported about the development of severe opportunistic infectious diseases like pneumonia, candidiasis, pulmonary aspergillosis etc in Covid-19 affected patients.^{6,7} There are also reports of development of mysterious fungal infection known as Mucormycosis or Black fungus in Covid-19 patients.⁸ Covid-19 patients in India also suffer with this epidemic disease (mucormycosis) with a reported case of 8848

till May 22, 2021.⁹ Here the current article reports signs, symptoms, diagnosis, treatment, prevention against black fungus.

Mucormycosis or black fungus

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.^{10, 11.}

Clinical pathogenesis

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.¹⁵ Mucormycosis also results in vascular thrombus and may lead to tissue necrosis.¹⁶

Studies suggested that Rhino cerebral Mucormycosis is most common among all other cases of Mucormycosis. It is most common in the patients with uncontrolled diabetes and leukemia. 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%.

In severe Covid-19 situation patient could develop dysfunction of immune system with decrease in lymphocyte counts and exponentially rise in inflammatory cytokines such as IL-6, IL-1 β , 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. Due to the severity of hyperinflammation or viral load physicians

preferred use of immunosuppressant or steroids as a life saving treatment in critically severe patients. A steroid reduces inflammation in the lungs besides these steroids also reduce immunity of the body and increases blood sugar level in both diabetic and normal patients. According to the physicians immunosuppressed patients are more likely to be affected with Mucormycosis or Black fungus.

The entry of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is possible via spike protein available on the envelope which binds with angiotensin converting enzyme 2 (ACE 2), which are available at pancreatic beta cells, lungs, kidney and small intestine. It is possible that entry of virus into pancreatic cells may damage beta cells and leads to insulin deficiency. Patients with hyperglycemia and ketoacidosis are more susceptible to get attacked by Mucormycosis moulds. Treatment of Covid-19 patient with immunosuppressant having uncontrolled diabetes mellitus and ketoacidosis are also at major risk for Mucormycosis as it leads to dysfunctional phagocytes causes impaired intracellular killing by oxidative and non-oxidative mechanism.²⁶

The pathogenesis of patients having diabetes mellitus in ketoacidosis also suggested that hyperglycemia and acidic pH (7.3–6.88) also leads to elevated free iron in the serum which is due to release of iron from the binding proteins. This free iron also promotes growth of Mucormycosis mould such as *Rhizopus arrhizu*, *Rhizopus oryzae*.²⁷

Moreover patients receiving deferoxamine are also more susceptible to get attacked by *Rhizopus* species while deferoxamine act as iron chelator. Studies suggested that Xenosiderophore, Siderophores of fungus has higher affinity for Iron than deferoxamine, so they easily detach iron from deferoxamine and provide it to fungus.^{28,29}

It was also pointed out that obese adipose tissues releases adipokines that modulate glucose metabolism by excessive release of inflammatory cytokines (IL-6, IL-8, TNF- α) and causes hyperinflammation.^{30,31} Adipose tissues in obese patient also induce mitochondrial production of reactive oxygen species (ROS).³² In hyperglycemic state, higher level of ROS will cause increased glycosylation and activation of protein kinase C.³³ Therefore, Covid-19 patient with obesity are also more prone to get attacked by Mucormycosis.

Patients with solid organ or bone marrow transplantation, 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.^{21,34,35} So here the inference is that Covid patient with lesser number of monocytes and neutrophils has higher probability to get infected by mucormycosis.

As discussed above, the probability of the development of Mucormycosis mould is mainly associated with patients suffering from diabetes mellitus, ketoacidosis, decreased immunity and patient's receiving immunosuppressant/corticosteroids as in case of Covid-19. The source of developing or inoculation of Mucormycosis moulds is mainly accompanied by contamination with water and soil.³⁶ In case of Covid-19 probably the source could be water for humidifier during oxygen therapy before inhaling inside by the patients. The infection can be life threatening and has a mortality rate of 38–80%.

Case report

The increasing cases of COVID-19 are thought to be responsible for the increasing cases of black fungus infection. Recently, a case of an 84-year-old patient with black fungus who was infected with the dreaded COVID-19 virus was reported in Egypt. His symptoms included severe knee pains and the inability to stand on his feet easily. However, the viral infection was easily treated without the patient experiencing kidney and lung failure. This led to being depressed and unconscious. In addition, the black fungus affected his right eye, and the patient described his experience as one of the most difficult diseases that afflict humans.

Methods

The information was gathered from the review of the relevant literature obtained from various databases, such as Science Direct, Springer, PubMed, Google, and Google Scholar.

COVID-19 and black fungus

The severe acute respiratory syndrome resulting from coronavirus 2 (SARS-CoV-2) disease in 2019 (COVID-19) has been connected to several opportunistic bacterial and fungal diseases. Furthermore, the predominant fungal pathogens causing co-infection in COVID-19 patients include Aspergillosis and *Candida*. Several incidences of mucormycosis in COVID-19 patients have recently been documented globally. Most cases so far have been reported in India. The environment includes an insufficient amount of oxygen (hypoxia), an increase in glucose (diabetes, new-onset hyperglycemia, and steroid-induced hyperglycemia), an acidic

medium (metabolic acidosis, diabetic ketoacidosis (DKA)), and an increased level of iron (high ferritins). Low white blood cells phagocytic activity (WBC) seems to help germinate the Mucorales spores in people infected with COVID-19.

According to the literature, people who contract coronavirus and undergo treatment are in danger of acquiring immunodeficiency⁴¹. The COVID-19 treatment drugs work to attack the virus while also having a significant impact on the immunity. Because of the increase in the proportion of cytokines secreted by the immune system to resist the coronavirus, which weakens the body's defenses, physicians are forced to give the patient steroids to suppress the immune system and reduce the secretion of cytokines. Still, both cytokines and steroids cause high sugar levels and a weak immune system¹².

Common symptoms of the black fungus infection

Black fungus infection is mostly a respiratory or skin infection. The symptoms of infection include symptoms of the respiratory tract and sinus irritation. Other symptoms and signs of black fungus infection include a cough, fever, headache, nasal congestion, and sinus discomfort¹³Swelling on one side of the face, headaches, fever, nasal or sinus congestion, and black lesions on the nose or upper portion of the mouth have also been reported as signs of black fungus infection. Other signs and symptoms of pulmonary (lung) mucosa disease include fever, cough, chest discomfort, and shortness of breath^{14 15}

The signs and symptoms of skin infection include blisters or ulcers. The afflicted region may turn black. There may also be discomfort, excessive redness in the afflicted areas, and swelling surrounding the infected wound¹⁶ Similarly, some of the intestinal mucosal disease symptoms include intestinal pain, nausea, and gastrointestinal bleeding. The early detection of the condition frequently leads to better treatment results^{15, 16, 14, 13, 12}.

Treatment

Anti-fungal medication is considered to be the most appropriate and effective method of treatment. The treatment plan, however, is very costly because the treatment period may be extended up to 8 months. Among the most popular compounds used is Amphotericin B, and the treatment period ranges from 5 days to 12 weeks until the patient reaches the point of recovery. In some severe cases, the treatment plan requires the removal of the parts that have been damaged to prevent the fungus spread and to maintain the patient's

health¹⁵. Isavuconazole has recently been used as a treatment with FDA approval. In addition, studies have proven the ability of hyperbaric oxygen to treat black fungus since high-pressure oxygen can raise the efficiency of the neutrophils in terms of eliminating the fungi²⁰

According to the US National Library of Medicine, all dead and contaminated tissue must be removed quickly. The palate, sections of the nose, or eye elements may be removed during surgery, resulting in deformity. However, if this procedure is not performed, the odds of survival are significantly reduced.

Antifungal medicine is also administered intravenously, commonly in the form of amphotericin B. Once the infection has been managed, the patient may be shifted to a different treatment, such as posaconazole or isavuconazole. When a person has diabetes, their diabetes levels must stay within a healthy range¹⁴.

Amphotericin B, Potassium iodide, miconazole, terbinafine, cotrimoxazole, hyperbaric oxygen, itraconazole, ketoconazole, and surgical debridement have been practiced in varying degrees of effectiveness¹⁵. Guarro *et al.* tested nine *Basidiobolus* spp. and eight *Conidiobolus* spp. isolates for susceptibility. *Basidiobolus* spp. exhibits lower geometric mean MIC values than those for *Conidiobolus* spp.: itraconazole at 1.8 vs. 11.3 lg mL, ketoconazole at 1.0 vs. 20.7 lg mL, miconazole at 3.9 vs. 11.3 lg mL, and amphotericin B at 2.7 vs. 3.1 lg mL. There is no clinical experience with voriconazole in the treatment of entomophthoromycosis. Over four years, the remarkable work of Krishnan *et al.* shows there to be a substantial improvement with potassium iodide at 40 mg kg per day in 9 of 10 patients with either basidiobolomycosis or conidiobolomycosis. Amphotericin B has been linked to clinical failure. Itraconazole or potassium iodide seem to be good first-line treatments. There is no one antifungal drug with a consistent antifungal action. *In-vitro* susceptibility testing may aid in treatment planning²⁰

II. CONCLUSION

The relationship between diabetes, COVID-19, and the black fungus is that diabetes weakens the immune system. This helps to attack the COVID-19 virus. The decline of the immune system facilitates secondary infections such as that of the mucous fungus, especially in the recovery phase from the virus. Most cases of the black fungus are closely related to COVID-19. Most COVID-19 patients are confined due to intensive care with the assistance of oxygen devices. In this case, the humidity is high, paving the way for easy infection by the fungi. As a result, researchers and healthcare

practitioners must quickly address mucormycosis infection by evaluating its impact and severity, particularly in COVID-19 victims. A multidisciplinary method can be performed including a timely diagnosis, antifungal therapy, and suitable surgical consultation or treatments. More evaluation of the impact of mucormycosis in COVID-19 ongoing and recovered patients is needed. Recovering patients should be recommended to stay in quarantine for some weeks. This is where the immunity can be improved through the use of follow-up tests to rule out any complications. Comparable precautions must be undertaken for people infected with the virus. Hand washing, masking, and social distancing should be followed by normal public health routines.

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