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Review Article

Mucormycosis (the black fungus) during COVID-19 pandemic: growing concerns of immunosuppressive therapy and uncontrolled diabetes mellitus

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ABSTRACT

In recent days rare but aggressive fungal disease in the form of mucormycosis has emerged and become a health concern mostly for the patients suffering from severe COVID-19 infection, poorly controlled diabetes mellitus, and patients who receive immunosuppressive therapies for diseases like malignancies. Many studies have demonstrated the relationship between COVID-19, immunosuppressive therapies, diabetes mellitus, and mucormycosis. In diabetes mellitus, poor glycemic control allows the fungi to produce pathogenesis. On the other hand, immunosuppression causes compromised neutrophil function that inhibits phagocytosis and the fusion of phagolysosome. Epidemiological data has proved that the incidence of mucormycosis from a global perspective has been on the rise and it has an association with an increasing number of diabetic cases in the world. In countries like India, Nepal, and Bangladesh where the number of diabetic and cancer patients has been growing constantly, mucormycosis could be a serious health concern in near future. Much more scientific studies, statistical analysis, and engagement of health experts are needed to combat the situation.

Keywords: Black fungus, Mucormycosis, COVID-19, Immunosuppression, Steroids, Diabetes mellitus

INTRODUCTION

Very recently, Mucormycosis, a rare fungal disease with a high rate of mortality and morbidity has emerged and attracted the attention of health scientists and clinicians especially from India.[1] Though rare, it has not been out of clinical documentation or case reports. Furbinger described the first case in 1876 in Germany when he had found a patient who died of cancer and the right lung of the patient had shown fungal sporangia and hyphae into a hemorrhagic infarct.[2] The first case of the disseminated type of mucormycosis was published by Arnold Paltauf in 1885. Paltauf named the condition "Mycosis mucorina" and draw images of the etiologic agent in the shape and form of rhizoid-like structure and sporangiophores.[3] This gave him the impression that the etiological agent might be Lichtheimia corymbifera. In course of time, the case identification has increased and reported.[4] Now in 2021, mucormycosis again has come to the limelight, to some extent, because of its association with severe COVID-19 infection, immunosuppressive therapies, and uncontrolled diabetes mellitus. This review aims to give emphasis and show the relationship between mucormycosis and those common and chronic clinical conditions that have been prevalent globally.

Mucormycosis – the black fungus

Mucormycetes are the etiological agent for mucormycosis which belongs to a group of molds that are present in the atmosphere and release spores that can be easily aerosolized and dispersed.[5] Taxonomic study revealed that the order of mucormycetes is Mucorales and the subphylum is Mucormycotina.[1] This order has many genera but Mucor species and Rhizopus are the commonest genera that produce infections in humans. The pathologic condition of mucormycosis can be categorized as gastrointestinal, pulmonary, rhinocerebral, cutaneous, disseminated, and other based on clinical presentations. Rare conditions connected with mucormycosis are osteomyelitis, endocarditis, peritonitis etc.[2]

Not all at risk

Analyzing the longstanding pattern of disease association, it is clearly understood that mucormycosis has been associated with a condition that leads to immunosuppression. People with malignancies especially those of hematological origin, stem cell or solid organ transplant, and people who have been on long-standing corticosteroid therapy are susceptible to develop the disease.[6] Recently it has been established that the commonest global risk factor of the disease has been uncontrolled diabetes mellitus.[7]

In very recent times, mucormycosis has been strongly associated with COVID-19 and it has become a matter of growing concern in countries like India. It may be because, several critical COVID-19 cases where cytokine storm has been suspected and established, have been treated with corticosteroids.[8] In very recent time, mucormycosis has been strongly associated with COVID-19 and it has become a matter of growing concern in countries like India. It may be due to the fact that, several critical COVID-19 cases where cytokine storm has been suspected and established, has been treated with corticosteroids.[8]

Epidemiological perspectives

Epidemiological data regarding mucormycosis have shown that the incidence of the disease has been on the rise in the form of invasive infection partly because of the availability of better diagnosis and recognition techniques and equipment and also in part because of using of immunosuppressive drugs in the treatment of malignancies and organ transplantation who are most susceptible to infection.[9,6] Statistical analysis of hospital discharge data from 2000 to 2013 in the US found that the incidence of hospital admission due to mucormycosis doubled from 1.7 to 3.4 per million residents which represent over 5% annual increase rate. Another study demonstrated that in 2014 the direct management cost of mucormycosis was 125 million USD for 1140 hospitalized patients.[10]

A week ago, the Indian Government declared mucormycosis as a health emergency after 153 patients have been diagnosed in Delhi. At the same time in Bangladesh two COVID-19 patients were diagnosed to be suffered from mucormycosis and both died. This may be the tip of the iceberg that we have seen due to the lack of proper diagnosis and statistical data. One study in Nepal demonstrated that COVID-19 positive cases were spreading more rapidly in the southern part of Nepal which has entry and exit points with India.[11] The same thing goes for Bangladesh as well where most cases positive for Delta variant of SARS COV-2 have been detected in border areas near India.

Outbreaks of mucormycosis may occur among high-risk patients admitted in health facilities or health care settings where infection might be linked to contaminated food and supplements, linen and dressings, leakage of water, poor air filtration in closed rooms like ICU, contaminated medical supplies, and even dental procedures. The mortality rate has been reported to be as high as 50% in these cases according to some studies.[12-14]

DISCUSSION

Mucormycosis and severe COVID-19 infection

A review considering case reports published in PubMed from the period of 1 December 2019 to April 2021 included information about risk factors, clinical presentations, diagnosis, treatment, and outcome of mucormycosis and COVID-19 demonstrated that among 47 of those reported cases 41 cases (about 87%) had well-documented mucormycosis with COVID-19.[15] It has been also demonstrated in other studies that COVID-19 patients, like any other serious infection, are susceptible to develop diabetic ketoacidosis if predisposed by diabetes mellitus. Previously in case of SARS COV1, evidence suggested that SARS COV1 damage pancreatic beta cell that causes acute diabetes mellitus and diabetic ketoacidosis. Based on this evidence researcher give a possible explanation of the diabetogenic effect of SARS COV2 on pancreatic islets that expresses a high level of angiotensin-converting enzyme-2 receptors. Another pathophysiological phenomenon that occurs is the development of insulin resistance resulting from a cytokine storm.[16] All these facts lead to the conclusion that, due to immunocompromised condition and use of corticosteroids, which hampers glucose homeostasis, mucormycosis in COVID-19 is much higher. Another possible fact that might be taken into consideration is that in many critical cases of COVID-19, clinicians use corticosteroids to combat cytokine storm and lung fibrosis. This results in immunosuppression of the patient and may lead to the development of mucormycosis.[8]

Mucormycosis and immunosuppressive therapy

One of the important risk factors for mucormycosis has been chronic administration of corticosteroids and

immunosuppressive agents. These agents have been used invariably in the management of autoimmune diseases, malignancies, and organ transplantations. It has been a fact that corticosteroids cause impairment in different cellular processes like migration, ingestion, and formation of phagolysosome fusion in macrophages. Moreover, it is evident that prolong use (>3 weeks) of a high dose of corticosteroid, is a risk factor for developing mucormycosis.[17] In addition, reports demonstrated that mucormycosis can be caused by short courses of corticosteroids as well.[18] A study in the ECMM revealed that 46% of patients who developed mucormycosis had received corticosteroids one month before diagnosis as a case of mucormycosis.[14] Jong et al published a review on global data and showed that 3% of diagnosed cases of mucormycosis had autoimmune diseases which Kennedy et al. found in Australia to be 12%.[19]

Mucormycosis and diabetes mellitus

The prevalence of DM in low- and mid-income countries has risen faster in comparison with high-income countries. One study showed that in India in the year 2011, the number of people aging from 20-79, who has been suffering from DM, was 61.3 million and it would increase up to 101.2 million in the year 2030.[20] Experts in the field are predicting the same for countries like Japan, Brazil, Indonesia, China, Egypt, and Mexico. This rise of DM cases will eventually raise the number of cases of mucormycosis.

Many studies have demonstrated that DM has been the leading cause of mucormycosis in the global setting. According to WHO "the global prevalence (age-standardized) of diabetes has nearly doubled since 1980, rising from 4.7% to 8.5% in the adult population. Globally, an estimated 422 million adults were living with diabetes in 2014, compared to 108 million in 1980".[21] Studies reported DM as a risk factor for mucormycosis in 75% of cases in Iran, 72% in Mexico, and 73.5% in India. Many Indian studies reported that in 12-31% of cases of DM, mucormycosis was the unmasking disease for DM.[7, 22]

The pathogenic study of mucormycosis reveals the importance of serum iron for producing disease in the human body. It has been reported that the rise of serum iron concentration is a risk factor for mucormycosis.[23] In normal conditions, iron is not available for the fungi to be used because in physiological conditions iron has been attached with ferritin and transferrin. But in diabetic ketoacidosis, the iron-binding capacity of ferritin and transferrin has decreased significantly due to acidosis and low level of pH. This favors the fungi to initiate infection and produce the disease.[24] On the other hand, in those cases of poorly controlled DM and chronic hyperglycemia, impairment of neutrophil functions has encountered which leads to defective neutrophil motility and phagocytic ability of neutrophils.[25]

It is a fact to be noticed that study reports showed Rhizopus as the commonest fungi present in patients with DM having mucormycosis and rhinocerebral mucormycosis is the most common type of mucormycosis in DM patients.[25,26]

Diagnostic options

The diagnosis of mucormycosis is multidimensional ranging from clinical features that lead to suspicion up to molecular diagnosis. Common clinical features due to mucormycosis are symptoms associated with pulmonary, rhinocerebral, and disseminated disease. Diplopia in a diabetic patient or pleuritic chest pain in a COVID-19 case or the neutropenic patient may be taken into consideration. The technologies and laboratory methods can help us identify the fungi.[27]

Table 1: Different methods of identification of mucormycosis.

Methods of identification	Remarks
Direct microscopy	Using KOH wet mounts
Fluorescent direct microscopy	Using fluorescent brighteners like Blankophor and Calcofluor White with KOH
Serology	ELISA Immunoblots Immunodiffusion tests
Histopathology	Biopsies of affected tissues Bronchopulmonary lavages
Culture	Identification of genus and species are possible. Grow on any carbohydrate substrate. Colonies appear within 24 - 48 hours
Molecular methods	DNA sequencing of ITS region PCR, qPCR, nested PCR can be done. Conventional PCR Restriction fragment length polymorphism analyses (RELP)

Diagnosis in different settings

It has always been a challenge to develop a diagnostic test for mucormycosis which would be rapid, cost-effective and at the same time preferably non-invasive. On the other hand, resources to detect genera and species without ambiguity varies widely from lab to lab, country to country. Molecular methods in the form of DNA sequencing of ITS region have been accepted as reliable, widely accepted, and recommended as a first-line diagnostic test for Mucorales.[28] Detection of fungi in the tissues can be done with the help of techniques like

qPCR, nested PCR, and RELP.[29] qPCR can detect mucormycosis from blood as rapidly as within 3 hours and shows high specificity. Also, it can diagnose the disease in immunocompromised patients earlier than imaging or conventional methods.[30-32] Therefore, they can be used for screening and monitoring high-risk patients and can increase survival rates.[33] Despite the development of diagnostic molecular techniques, histopathology, culture, and direct microscopy remain essential tools for less equipped laboratories. The following chart shows the test hierarchy according to sensitivity, specificity, and reliability parameters.

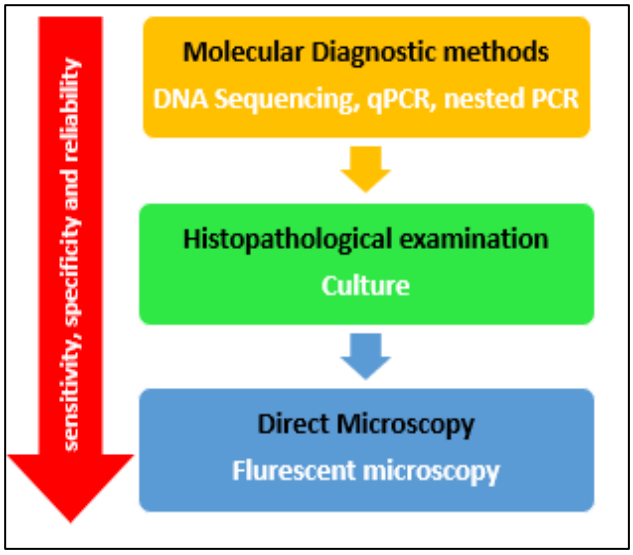

Figure 1: Test hierarchy according to sensitivity, specificity, and reliability.

Points to ponder the management

We are not going to discuss in detail all the treatment modalities as discussion on treatment modalities is not in the scope of this review. Successful treatment depends on quite a few factors including but not limited to reversal or discontinuation of the predisposing factors that have been the underlying cause in the first place. Other measures could be like correction of metabolic abnormalities like diabetic ketoacidosis, other kinds of acidosis, etc. Immunosuppressive agents and corticosteroids should be tapered and to the lowest possible dose as soon as the diagnosis has been established.[34, 35]

Early diagnosis and starting of appropriate antifungal drugs in optimum dose should be considered. This is since early intervention with proper antifungals can minimize the devastating effect, produce a better outcome, and increase the survival rate.[36] Including voriconazole, most of the antifungal agents were found ineffective in vitro studies. Amphotericin B is the drug of choice as it has been proved to be effective in most cases.[37] In 2016, European Conference on Infections in Leukemia (ECIL-6) proposed a lipid formulation of Amphotericin B at a dose of 5-10 mg/kg/day as first-line therapy.[34] In the case of other antifungals such as triazoles like posaconazole and isavuconazole, the appropriate dose has yet to be established.[38]

CONCLUSION

Mucormycosis has become a global concern now a day in the COVID-19 pandemic especially for those countries that have a high prevalence of diabetes mellitus. There has been a close relationship between mucormycosis and immunosuppressive therapy. On the other hand, severe COVID-19 infection has also been considered as a risk factor for mucormycosis. It is mostly because severe COVID-19 infection is a predisposing factor for hyperglycemia and at the same time in most cases of cytokine storm, corticosteroids have been used. In the perspective of South Asia including India, Nepal, and Bangladesh, the number of diabetic cases as well as the number of cancer patients treating with immunosuppressive therapies is increasing day by day. The second wave of COVID-19 also hit India and Bangladesh badly. In near future, cases of mucormycosis might become a serious health concern. More studies, case reports, and statistical analyses are needed to prepare ourselves for the upcoming battle against this rare but emerging notorious black devil.

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