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Review article

Black Fungus Hitting Covid-19: Mucormycosis

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ABSTRACT:
Mucormycosis is a rare but potentially fatal fungal infection if inadequately treated. It was found to be triggered by the use of steroidal therapy in severe and critically ill COVID-19 patients.Other factors like combination of high blood sugar, immune dysregulation, usage of immunosuppressant medications and thrombotic occlusion of vessel provides a breeding ground for this opportunistic infection. Special attention was needed to focus on identifying the signs of mucormycosis such as sinus pain, nasal obstruction on one side of the face, one-sided headache, swelling or numbness, toothache, and loosening of the teeth. This fungal infection also leads to discoloration or reddening of the nose, blurred or double vision, chest pain, coughing up blood and difficulty breathing has additional heavy burden for COVID-19 patients. Amphotericin B and its lipid formulations and posaconazole were the only antifungal drugs available to treat mucormycosis. The antifungal armamentarium recently enlarged with the development of is avuconazole. The first-line recommended antifungal agent is liposomal Amphotericin B or Amphotericin B lipid complex. Many incidences proved that COVID-19 was found to be associated with the significant incidence of secondary infections and the triad of corticosteroid use, acute respiratory syndrome and uncontrolled diabetes mellitus have been clearly responsible to cause the significant increase in mucormycosis. Early diagnosis is very important in order to promptly initiate necessary therapeutic interventions.

Keywords: COVID-19, mucormycosis, infection, steroid, antifungal.

1. INTRODUCTION

Mucormycosis is an infection caused by a group of filamentous molds within the order Mucorales. Infections may occur from ingestion of contaminated food, inhalation of spores into the lungs or nares, or inoculation into disrupted skin or wounds. In developed countries, mucormycosis primarily occurs in severely immunocompromised hosts e.g. in patients with hematological malignancies, organ transplantation, neutropenia, autoimmune disorders, or other impairments in immunity [1].

Recently the mucormycosis, extremely rare fungal infection, emerging as a matter of concern in COVID-19 which itself is a life-threatening disease and various factors, like diabetes, especially when complicated by ketoacidosis, immunosuppressive therapy, previous respiratory pathology, , nosocomial infection sources and systemic immune alterations of COVID-19 itself may lead to mucormycosis, Often referred to as “black fungus”, the incidence of mucormycosis has risen more rapidly during the second wave as compared to the first wave of COVID-19 in India, with at least 14872 cases as of 28th May 2021 [2,3].

2. BRIEF PATHOPHYSIOLOGY OF MUCORMYCOSIS

COVID-19 has been studied and shown to enter the cell via the ACE2 and TMPRSS-2 receptors. While ACE2-R is a ubiquitous receptor inside the body, it has higher rates of expression in respiratory, renal, and gastrointestinal epithelium. TMPRSS-2 receptors are similar: they are present on many epithelia but especially on that of respiratory and gastrointestinal. One of the characteristic features of mucormycosis is its angio invasive property, resulting in vascular thrombosis and ultimately tissue necrosis. Ketoacidosis and deferoxamine are known to predispose to mucormycosis, revealing the importance of hyperglycemia, iron, and acidifying ketone bodies in mucorales virulence. Angioinvasion was reported to be related to the interaction between a spore-coating protein family (CotH) on Rhizopus spp. surface and endothelium glucose regulator protein 78 (GRP78) expressed at the surface of endothelial cells. This interaction triggers host cell

injury and subsequent fungus hematogenous dissemination. Elevated levels of serum glucose, iron, and ketone bodies increase fungal growth and induce the expression of GRP78 and CotH, resulting in increased ability of Rhizopus to invade host tissues and explaining the susceptibility of diabetic and deferoxamine-treated patients to mucormycosis. However, it should be noted that the majority of studies on virulence and the association between ketoacidosis and the occurrence of mucormycosis have been conducted with Rhizopus species [4-6].

3. CAUSES OF MUCORMYCOSIS

Mucormycosis is considered as a third most important disease in Europe among haematological patients besides aspergillosis and candidiasis, Mucormycosis can be caused as the following types of diseases: (i) Rhinocerebral mucormycosis, which can infect the sinuses and the brain leading to fever, swelling of one side of the facial organ, black lesions inside the mouth/outside the face, headache and sinus congestion; (ii) Pulmonary mucormycosis, which mainly infects the lung leading to chest pain, disturbance in breathing, fever, and cough; (iii) Cutaneous mucormycosis causes local skin infections leading to ulcers or blisters, redness, and swelling of the infected skin region; (iv) Gastrointestinal mucormycosis, which is uncommon in adults, but occurs more often in premature neonates leading to nausea, vomiting, gastrointestinal bleeding, and abdominal pain; (v) Disseminated mucormycosis, which occurs in patients suffering from multiple medical complications imminent the symptomatic discrimination of mucormycosis from further infectious diseases; and (vi) Uncommon presentation as renal infection. Doctors tend to believe mucormycosis, which has an overall mortality rate of 50%, may be triggered by the steroids, used as a life-saving treatment for severe and critically ill Covid-19 patients. Steroids are in usage since decades as has been the diabetic population but we haven't seen such gush in opportunistic fungal infections. In nutshell, a combination of high blood sugar, immune dysregulation because of disease itself and/or usage of immunosuppressant medications and thrombotic occlusion of vessels provides a breeding ground for infection and also supports the fact that anticoagulants are needed to prevent thrombosis [7,8].

Recently, the Indian Council of Medical Research (ICMR) suggested that doctors and medical facilities need to pay special attention to signs of mucormycosis such as nasal obstruction on one side of the face, sinus pain, one-sided headache, numbness or swelling, toothache, and loosening of the teeth. Mucormycosis usually leads to discoloration or reddening of the nose, chest pain, blurred or double vision, coughing up blood and difficulty breathing which is an additional very heavy burden for COVID-19 patients. The International Diabetes Federation has stated that India has a very high incidence rate of type 2 diabetes (8.9% adults, 77 million patients) [9].

4. RELEVANT LITERATURE ON MUCORMYCOSIS

In a recent literature, a cross-sectional study was conducted amid 50 COVID doctors from the department's outpatient pool of COVID patients, distributing questionnaires to all subjects of different age groups and it was seen that doctors prescribed more methylprednisolone and dexamethasone medicine than steroid medicines to corona patients. Inthis research, most side effects were observed for corona patients taking methylprednisolone and dexamethasone drugs. This research had shown that overdose of methylprednisolone and dexamethasone drug intake by diabetes patient has serious eye effect and causes black fungus [10].

Till 25th May 2021, there are about 11717 cases found of mucormycosis that have been reported from India with more than 200 casualties. In another study, 62/806 (8%) patients had secondary bacterial or fungal infections during hospital admission. There was widespread use of broad-spectrum antibiotics, with as many 1450/2010 (72%) of patients receiving these drugs, often with no underlying evidence of infection [11,12].

Current guidelines in India suggest intravenous methylprednisolone 0.5-1 mg/kg/day for three days in moderate cases and 1-2 mg/kg/day in severe cases. The National Institute of Health recommends the use of dexamethasone (6 mg per day for a maximum of 10 days) in patients who are ventilated or require supplemental oxygen but not in milder cases. The guidelines specifically mention the risk of developing a secondary infection [13-15].

In a 2021 study, thirteen patients were presented with COVID-19 associated mucormycosis (CAM). The median age was greater in non-survivors (49.5 years), with a higher odds of death (23.8) in those with severe COVID-19, having overall mortality rate of 64.3%. Moreover, diabetes mellitus was present in 61.5% of patients with a mortality of 75%. About 11 (84.6%) patients had received prior steroids for COVID-19. The incidence of hyperglycemia at admission was equal among both survivors and non-survivors [16].

In March 2021, cases of 41 patients of COVID-19 associated mucormycosis has been reported worldwide and majorly 70% were from India. There have been 2245 cases reported and 120 deaths from the infection in Maharashtra state. As of June 5, 2021, Rajasthan reported 2651 cases and 85 and Telangana reports around 50 cases daily. In Tamil Nadu, till June 9, 2021, total cases of mucormycosis reported being to be 1196. The mucormycosis stemming from COVID-19 patients has been more commonly observed in patients with a history of diabetes mellitus and 95% of individuals with severe or critical COVID-19 [17].

In another study, sixteen patients were (M: F 13:3) with a mean age of 46·5 years (SD, 14·5) were diagnosed with mucormycosis and were included in the study. Fifteen patients had one or more than one co-morbidity, most commonly chronic kidney disease (n = 2), solid-organ transplantation (n = 1), uncontrolled diabetes mellitus,

haematological malignancy (n = 1), chronic granulomatous disease (n = 1) and decompensated chronic liver disease (n = 1) Three out of twelve diabetic patients had presented with diabetic ketoacidosis. Two patients were diagnosed with mucormycosis during convalescence from COVID19, whereas the rest had features suggestive of mucormycosis even before the diagnosis of COVID19. The median duration of symptoms persisting was 15 days (range, 6–60 days). All patients were managed with Liposomal Amphotericin B (Fungisome) with or without surgical debridement. It was initiated at a dose of 3 mg/kg and escalated to 5 mg/kg if tolerated well. Out of the sixteen patients, five patients needed admission to the intensive care unit (ICU), two patients due to diabetic ketoacidosis with severe metabolic acidosis, two due to severe COVID19, and one due to sudden drop in sensorium (due to progressive mucormycosis). The median duration of hospitalization was 40.5 days. There were six (37.5%) mortalities in this cohort, all of them attributable to mucormycosis. Seven patients (43.75%) patients have been discharged with step-down long-term maintenance therapy with oral Posaconazole tablets (at a dosage of 300 mg OD). Two patients (6.13%) were still admitted to underwent the treatment [18].

In a research article, overall, 101 cases of mucormycosis have been reported in people with COVID-19, of which 82 cases were from India and 19 from the rest of the world. Mucormycosis was mainly seen in males (78.9%), both in people who were active (59.4%) or recovered (40.6%) from COVID-19. Pre-existing diabetes mellitus (DM) was present in 80% of cases, while concomitant diabetic ketoacidosis (DKA) was present in 14.9%. Corticosteroid intake for the treatment of COVID-19 was recorded in 76.3% of cases. Mucormycosis was most common followed by rhino-orbital (56.7%) involving nose and sinuses (88.9%). Mortality was noted in 30.7% of the cases [19].

5. TREATMENT OF MUCORMYCOSIS

For the treatment of mucormycosis, epidemiological aspects and some clinical (concomitant diabetes, sinus disease, occurrence under voriconazole therapy) and radiological (reverse halo sign on chest CT-scan) factors may help to suspect mucormycosis, the diagnosis remains difficult and biopsy of the lesion is often required. In immunosuppressed patients with a previous diagnosis of mucormycosis (n = 3), surgery in combination with secondary antifungal prophylaxis successfully prevented recurrence [20,21].

According to a retrospective study on 30 patients combined with a literature analysis of 225 patients with mucormycosis, surgical debridement of lung involvement was associated with a reduction of mortality from 62% to 11%. Procedures were lobectomy, pneumonectomy or wedge resection and patients with non-disseminated disease were more likely to be treated surgically [22].

Amphotericin B (Amb) and its lipid formulations and posaconazole were the only antifungal drugs availablewith in-vitro activityagainst mucorales. The antifungal armamentarium recently enlarged with the development of isavuconazole. The first-line recommended antifungal agent is liposomal Amb (L-Amb) or Amb lipid complex (ABLC). Murine models suggest that liposomal amphotericin B is more effective than the deoxycholate formulation against mucormycosis, and that for liposomal amphotericin B and amphotericin B lipid complex efficacy was dose-dependent [23,24].

In patients with mucormycosis, surgery whenever possible is strongly recommended along with the medical treatment. Immediate treatment initiation is strongly recommended to increase survival rates. Liposomal amphotericin B is the drug of choice and the dose should be at least 5 mg/kg/day. The use of amphotericin B deoxycholate is discouraged [25]. The duration of the first-line antifungal treatment is still a matter of discussion and should be determined on an individual basis and adjusted based on the underlying condition of the patient. Some authors proposed a lipid Amb treatment for at least three weeks and when there is clinical and radiological improvement, a consolidation by posaconazole can be started. However, it could possibly be guided by negative PCR and therefore shortened for some patients [23].

Corticosteroids and other immunosuppressive drugs should be tapered as soon as possible and to the lowest possible dose. Early diagnosis is crucial in order to promptly initiate therapeutic interventions necessary for preventing progressive tissue invasion and its devastating sequelae, minimizing the effect of disfiguring corrective surgery, and improving outcome and survival. Surgery when needed and possible must be very aggressive. Not only necrotic tissues but also surrounding infected healthy-looking tissues should be eliminated, as the speed of the extension of the infection by the Mucorales hyphae is enormous. Surgery is particularly useful in soft tissue infection and in rhino-orbito-cerebral infection. In cases of a single localized pulmonary lesion, it may be helpful. It is obviously impossible in cases of disseminated mucormycosis or when infection of difficult-to-reach organs (i.e., certain parts of brain or lung parenchyma close to great vessels) exists. In cases with a successful outcome, plastic surgery will be used to correct disfigured body areas[26].

6. PROGNOSIS OF MUCORMYCOSIS

Prognosis is poor in most cases in spite of aggressive therapy but it can be enhanced comparatively by early diagnosis and prompt treatment. The mortality rate depends upon the severity and expansion of the disease. Mortality in rhinocerebral form is high around 30% to 70%, in disseminated form is up to 90%, and with AIDS has up to 100%. It is demonstrated that the survival rate of a combination of surgical debridement and antifungal therapy is greater (70%) than the surgery (57%) and chemotherapy alone (61%).One study concluded that survival of patients is

85% when managed within 5 days of diagnosis as compared to 49% when treatment initiated after the 6th day of diagnosis. The overall mortality rate amplifies from 145 to 80%, depending upon the individual status and time of diagnosis and treatment of the disease. It is concluded that the mortality rate is higher in predisposed and cerebral involved patients than in patients without predisposing factors [27].

7. CONCLUSION

COVID-19 is mainly linked with the significant incidence of secondary infections and the triad of corticosteroid use, acute respiratory syndrome and uncontrolled Diabetes mellitus have been at apparent for the significant increase in mucormycosis. Early diagnosis is pivotal in order to promptly initiate therapeutic interventions that are necessary. Physicians should be aware of the use of therapeutic agents that are to be monitored to achieve therapeutic effect must be at the lowest and for the shortest duration.

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