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COVID-19 associated Mucormycosis- An overview

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ABSTRACT
Mucormycosis, also known as the black fungus, made severe chaos in India during the second wave of the COVID-19 epidemic by its sudden and catastropic surge with high mortality rate.A rare type of opportunistic and aggressive fungalpathogen called mucormycetes causes this serious life threatening infection in patients with compromised immune system. The predisposing factors are increase in the number of poorly managed Diabetes Mellitus (DM), organ transplantations, patients with malignancy and frequency of natural disasters and trauma. In India, there has been reports of increase in cases of rhino-orbital mucormycosis in people with coronavirus disease 2019 (COVID-19). The exact cause of its sharp rise suddenly and specifically during the second wave remains debatable. DM is an independent risk factor for both severe COVID-19 and mucormycosis.However, an early detection of mucormycosis is essential since it enhances the likelihood of the condition to get better. An immediate antifungal therapy, surgical debridement where necessary, and the reversal of underlying risk factors can be used to treat mucormycosis effectively.

KEY WORDS: Mucormycosis, COVID-19, CAM, Diabetes mellitus, Rhizopus

I. INTRODUCTION

Mucormycosis also known as the black fungus (Ong et al. 2021) is a fatal, rapidly progressing fungal infection that usually affects patients with altered immunity. It is found to be an opportunistic infection as these moulds are usually omnipresent in the hot and humid areas of the tropics. Most of them are non-pathogenic, but some of them belonging to class Zygomycetes like Rhizopus oryzae are known for causing life-threatening infections.In the year 1885, zygomycosis or phycomycosis was first described by Paltauf (Paltauf, 1885) and later coined as 'Mucormycosis' in 1957 by Baker (Baker, 1957) an American pathologist for a violent infection caused by Rhizopus, under order Mucorales and sub phylum Mucoromycotina. It is considered as the third most common invasive mycosis that occurs predominantly due to inhalation of the released sporangiospores and occasionally by inoculation of wounds or by ingestion of contaminated food(Petrikkos et al. 2012).

The most common etiological agents associated with mucormycosis are Rhizopusspp.,Mucorspp.,Lichtheimiaspp. and few rarely tagged genera of other Mucorales, such as Rhizomucor, Saksenaea, Cunninghamella and Apophysomyces(Petrikkoset al. 2012). In India,Rhizopus is the most common species along with few emerging species likeApophysomyces elegans, A. variabilis, Rhizopus homothallicus, Thamnostylum lucknowense and Mucor irregularis(Chakrabarti et al.2010, Hemashettar et al.2011 and Xesset al. 2012). On the other hand,Rhizopus spp. (34%), Mucor spp. (19%), and Lichtheimia spp. (19%) are predominant species in European countries (Skiadaet al. 2011 and Chakrabarti et al.2014). While most of those serious fungal infections are caused by the Genus Candida and Aspergillus, where but Zygomycetes has now emerged as the third most important pathogen among the immunocompromised patients (Chakrabarti et al. 2009; Roden et al. 2005; Perfect et al. 1996 and Ponton et al. 2000). However, in spite of the geographical variation Rhizopus arrhizus is considered to be the predominant causative agent worldwide (Skiada et al. 2011).

EPIDEMIOLOGY:

Health-care-associated mucormycosis has become more common in recent years (Rammaert et al. 2012). A wide range of microbial co-infections may exist with comorbidities like

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Diabetes mellitus, pulmonary disease, heart disease, renal disease, etc.The time course for mucomycosis is less than four weeks, but most of the mucormycosis cases either have been missed or under reported. A recent study had reported that the frequency of occurrence of mucormycosis was found to be doubled in France within a period over 10 years (1997-2006) (Bitar et al. 2009). However, existence of different epidemiologies has been noticed when compared between developed and developing countries. There has been a noted difference in the prevalence of risk variables disease and mucormycosis causative agents between Western and Asian countries (Jeong et al. 2019). Also, the incidence of mucormycosis is increasing due to increase in the number of organ transplantations, patients with malignancy, patients with DM, and frequency of natural disasters and trauma (Baldin et al. 2017).

Although the disease incidence is rising globally, however higher incidence rate has been observed in India as well as in China in patients with diabetes mellitus. According to a study conducted in a tertiary health centre in North India between 2000 and 2014, rhino-orbito-cerebral mucormycosis was the most prevalent form of mucormycosis is rhino-orbito-cerebral mucormycosis (44–49%), followed by cutaneous (10– 16%), pulmonary (10–11%), disseminated (6–11.6%), and gastrointestinal (2–11%) mucormycosis (Singh et al. 2021). It has been reported that children with kwashiorkor (protein-calorie malnutrition) specially develops gastrointestinal mucormycosis along with non-specific symptom like intra-abdominal abscess. However the disease showing such symptoms is rarely found in United States. Persons with hematological malignancies are prone to highest incidence in acute myelogenous leukemia, the incidence rate is found to be 2-8% (Petrikkos et al. 2012). The disease is thought to strike predisposed people, with different clinical manifestations associated with different underlying conditions, such as rhino-orbito-cerebral type in Diabetic Ketoacidosis (DKA), pulmonary and disseminated infection in patients with haematological malignancies and bone marrow transplantation, and gastrointestinal in patients with malnutrition and cutaneous lesions following trauma. (Singh et al. 2021).In Asia, DM is the most common risk factor, whereas in Europe and the United States, hematological malignancies and organ transplants seem to be the most common risk factors(Chakrabarti et al. 2006 and Skiada et al.2011).In developing country like India with diabetes and trauma being the predisposing factors, number of cases are 14 per100000 population and on the other hand thecases with hematological malignancies and organ transplant have prevalence of 0.01 to 0.2 per 100000 population in Europe and the United States of America (Ruhnke et al. 2015, Rees et al. 1998 and Chakrabarti et al. 2014).

In addition, since the inception of COVID-19 in late 2019s, has led to the devastation of the human health worldwide and at the same time, the rise of fatal fungal infection of mucormycosis, has put the lives of COVID-19 patients further at high risk (Revannavar et al. 2021 and Werthman-Ehrenreich, 2021).WHO declared the outbreak of COVID-19 as a global pandemic on March 11, 2020 which is caused by the Severe Acute Respiratory Syndrome Coronavirus 2 or SARS-CoV-2 (Cucinotta and Vanelli,2020, Ghazi et al. 2021). COVID-19 is potentially linked to a high rate of secondary bacterial and fungal infections, due to immune dysregulation. Furthermore, as part of the COVID-19 armamentarium, uncontrolled application of broad-spectrum antibiotics, steroids and monoclonal antibodies, can lead to fungal diseases or worsen pre-existing fungal diseases (Ghazi et al. 2021). Furthermore, the treatment regimen for COVID-19 and other diseases include prolonged use of immunosuppressants, which may interplay with the other factors and cause Covid-19 Associated Mucormycosis(CAM). Thereby,mucormycosis andCOVID-19 leading to comorbid conditions has caused worsening of the of infection and mortality rates.

According to surveys, patients infected with COVID-19 are also susceptible to other different fungal diseases like Aspergillosis and Candida, which are common in immunocompromised patients (Kubin et al. 2021). Although the cases of mucormycosis are more in India, COVID-19 Associated Pulmonary Aspergillosis (CAPA) has received enough attention internationally. Unlike CAM, CAPA is mostly seen only in severely affected COVID-19 patients. The focal reason that appears to be facilitating mucorales spores germination in COVID-19 patients is due to low oxygen (hypoxia), high glucose which occurs due to irrational use of steroid in treatment of COVID-19 and thus results in blood sugar spike in patients by interfering with pancreatic function diabetes, new onset of hyperglycemia, steroid-induced hyperglycemia. The acidic medium due to metabolic acidosis andDKA, high iron levels (increased ferritins) and decreased phagocytic

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activity of white blood cells (WBC) due to immunosuppression in patients with Covid (SARS-CoV-2 mediated, steroid-mediated or background comorbidities) coupled with several other shared risk factors including prolonged hospitalization with or without mechanical ventilators. Also,due to progressive viral pneumonia maximum alveoli in the lungs as well as the endothelial tissues are damaged that serves as niche for the invasive fungal infection spontaneously to set in not only for aspergillosis and mucormycosis (Vanderbeke et al. 2018 and Ajmal et al. 2018) but also invasive fusariosis or invasive candidiasis (Alanio et al. 2020 and Poignon et al. 2020).

RISK FACTORS:

Several host related factors associated as predisposing condition such as neutropenia, ketoacidosis, solid organ transplant (SOT), chronic respiratory diseases, corticosteroid therapy, hyperglycemia and iron overload etc. enable them to aggravate the rapid spread of infection. (Hamiloset al.2011 and Petrikkoset al.2018). Apart from these host related factors, hospital related factors such ascontaminated air filters and several medical devices like tongue depressors, wound dressings, transdermal nitrate patches, allopurinol pills as well as intravenous catheters also contribute to this infection (Petrikkoset al. 2003).

One of the major factors favoring infection with CAM is diabetes. Patients with DKA are more likely to develop rhino-cerebral mucormycosisespecially in the setting where health care access is limited (Greenberget al.2004 and Gonzalezet al.2002).All type-I, type-II and secondary DM are found to be predisposing factors whereas rare involvement of metabolically controlled diabetes has been reported (Bhansaliet al.2004). However,type-II diabetes has been implicated as the main cause up to 44–88% cases and nearly half of the cases were diagnosed with ketoacidosis (Chakrabarti et al. 2006,Chakrabarti et al. 2009 and Nithyanandam et al. 2003). Although 36%-88% cases are reported so far but incidence is found to be decreased due to use of statin drug against metabolic syndromes in many western countries (Chamilos et al.2006 and Reedet al. 2008). Mishra et al. 2021 reported in a study conducted in India that 87.5% of the CAM patients had DM as most common co-morbidity.In healthy individuals, transferrin, ferritin, and lactoferrin are blood plasma protein usually bound to iron that makes these iron molecules unavailable for mould growth. However, ironacquisition is crux for the growth of most species of pathogenic zygmocetes.In patients with DKA, iron is released from transfer proteins into the serum due to the low pH of blood. The serum of normal healthy individual inhibits growth of mucorale but due to acidosis condition under low pH transferrin cannot bind the metal ions and thereby allowing the Rhizopus spp. to utilize for their growth (Artiset al.1982). Also, in diabetic patients, defensive function of alveolar macrophages is found to be impaired which otherwise inhibit the Rhizopus spores from geminating in normal healthy individuals(Waldorf et al.1984). Even impaired neutrophil in diabetics also contribute to mucormycosis that leads to defective intracellular killing of microorganisms by both oxidative as well as non-oxidative mechanisms(Mowat et al. 1971).

Patients with either neutropenia or bone marrow transplantation are also at greater risk of suffering from pulmonary mucomycosis. Data says almost 7.2%-8% stem cell transplant recipient and 2% solid organ transplant recipients are under risk of mucormycosis infection (Neofytoset al. 2009 and Kontoyiannis et al. 2010).Few study reports say that patients with solid tumors rarely develop the infection but can be seen in other hematological conditions associated diseases such as aplastic anemia and sideroblastic anemia, multiple myeloma, myelodysplastic syndrome etc(Kontoyiannis et al. 2000 and Mileshkin et al. 2001). On the other hand according to few studies, it has been stated that if the patients are treated with high dose of steroids or antithymosite globulins due to acute rejection during solid organ transplantation even such patients are also at risk of suffering from mucormycosis (Jimenez et al. 2002 and Nampoory et al. 1996).

In case of immunocompromised individuals, mucormycosis has occupied 3rd position as common opportunistic pulmonary mycosis (Fanta et al. 1981). In general the Human deficiency viruses are not appeared to cause mucormycosis infection since the neutrophils are still functional and contribute to defense against mucorales. But it can occur when the patients are treated with intravenous drugs and may develop cerebral mucormycosis (Van den Saffele et al. 1996, Hejny et al. 2001 and Hopkins et al. 1994).

Patients with deferoxamine therapy can make the iron molecules available for the organisms by chelating these molecules as these are required for the growth of moulds. Hence, patients receiving hemodialysis are at higher risk of suffering from disseminated mucormycosis since they receive deferoxamine therapy at the same time(Van Cutsem et al. 1989 and Boelaert et al.

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1988). Moreover, the half-life of deferoxamine therapy is also long. According to a report byDaly et al. 1989 it was found that more than one half patients usually suffered from disseminated mucormycosis and one quarter patients suffered from rhino cerebral disease. But now a days by using alternative option like therapeutic erythropoietin has decreased the risk of mucormycosis involvement as well as frequency of blood transfusion. Severe iron overload is also seen in patients who receive bone marrow transplant.Several complications like paranasal sinus mucormycosis have been reported during and post COVID infection which is a recent globally concerned issue.

TIMELINE OF OCCURANCE:

Even before the spread of Covid-19, mucormycosis cases were much more prevalent in India than in other countries, owing to the high number of diabetic patients who do not have regular health check-ups(Mishra et al. 2021). During the second wave, the number of mucormycosis cases reached an'epidemic within a pandemic' level, as described by some experts(Ong et al. 2021).In the second wave, CAM was initially described in a 15-year-old kid who received effective treatment for Covid-19 after which multiple states, including Gujarat, Maharashtra, Rajasthan, Karnataka, Andhra Pradesh, Haryana, and Telangana, have recorded a high number of cases throughout time.From May 5-July 12, 2021, 41,512 cases and 3,554 deaths were attributed to this rare, and life-threatening fungal infection. The majority of those cases occurred during active SARS-CoV-2 outbreaks in India, prompting the Central Government of India to declare a mucormycosis epidemic on May 10, 2021(Hagen, 2021).A multi-center retrospective study conducted in India from November to December 2020 revealed that the prevalence of mucormycosis in Covid-19 patients was 65.2 %, which was associated with DM and incorrect glucocorticoid administration (Patel et al. 2021).

DIAGNOSIS:

Early diagnosis of mucormycosis is crucial since it increases the likelihood that the condition will improve.Therefore, it is important to develop laboratory techniques to meet the needs for an accurate diagnosis.The two main methods for identifying mucormycosis are direct microscopy of culture using optical brighteners like Blankophor and Calcofluor as well as histopathology of various clinical specimens using hematoxylin and eosin sections, periodic acid-Schiff staining and Grocott-methenamine Gomori's silver staining.(Frater et al. 2001; Lass-Florl et al. 2007 and Skiada et al. 2018). Presence of white in clinical specimens allows a rapid presumptive diagnosis of mucormycosis (Lass-Florl et al. 2007and Lass-Florl, 2009). The hyphae of mucorales have a varied width (6 to 25 m), are nonseptate or pauci-septate, and exhibit an erratic, ribbon-like appearance. (Monheit et al. 1984). The angle of branching varies and includes wide-angle (90°) bifurcation (Skiada et al. 2018). Inflammation may be neutrophilic or granulomatous, and is dominated over tissue histopathology, however, inflammation seems to be absent in a few cases like immunosuppressed patients (Spellburg et al. 2005a).

Serological assays such as immunoblots, immunodiffusion tests and enzyme-linked immunosorbent assays have been studied with varying degrees of success. (Sandven et al. 1992; Wysong et al. 1987 and Jones et al. 1978).However, ongoing research in molecular diagnostic tools which includes molecular based assays like conventional polymerase chain reaction (PCR), restriction fragment length polymorphism analyses (RFLP), DNA sequencing of defined gene regions, and melt curve analysis of PCR products are found to be promising for more-rapid diagnosis (Nagao et al. 2005; Larche et al. 2005; Machouartet al. 2006; Nyilasi et al. 2008; Springer et al. 2016 and Kasai et al. 2008).The majority of the molecular assays target either the internal transcribed spacer or the 18S rRNA genes (Alvarez et al. 2009 and Lackner et al. 2014).Recently, 2 real-time quantitative polymerase chain reaction assays targetting the 28S rRNA gene of Rhizopus, Mucor, and Cunninghamella species could successfully detect circulating DNA in rabbits with experimental pulmonary mucormycosis (Kasai et al. 2008).

Also, refinement of radiographic techniques for distinguishing mucormycosis from other diseases is an important area of future studies. Techniques like computed tomography is useful for early detection and differentiation of pulmonary mucormycosis from other fungal diseases like Aspergillosis, particularly in cancer patients on the basis of sinusitis, presence of multiple (≥10) nodule and pleural effusion (Chamilos et al. 2005). On the other hand, magnetic resonance imaging is more sensitive in comparision to computed tomography for detection of mucormycosis in cases of orbital and central nervous system involvement (Reed et al. 2008).

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TREATMENT STRATEGIES:

After an early diagnosis, a treatment plan for mucormycosis may be initiated, followed by the reversal of underlying risk factors, surgical debridement where necessary, and an efficient antifungal therapy (Spellberg et al. 2005b). Immunosuppressive medications like corticosteroids, should be discouraged or administered at low dosages if unavoidable. In conditions like diabetes and ketoacidosis, aggressive treatment to rapidly restore euglycemia and normal acid-base status is very critical (Spellberg et al. 2009).

Surgical management was found to be an independent variable in regard to favorable outcome among patients with mucormycosis in a logistic regression model (Roden et al. 2005). However, surgery when needed and possible must be very aggressive with removal of necrotic tissues along with surrounding infected healthy-looking tissues, as the speed of the extension of the infection by the Mucorales hyphae is enormous(Skiada et al.2018). Debridement of necrotic tissues is essential for the complete eradication of mucormycosis because they prevent antifungal medicines from reaching the infection site.Certain treatment strategies against mucormycosis based on preclinical trial can have the potential to improve outcomes of mucormycosis by use of anti-fungal agents like polyenes, azoles and certain combination drug therapies like echinocandins, iron chelation therapy, posaconazole combination therapy and other adjunctive therapies (Spellberg et al. 2009).The response treatment to antifungal agents is generally dependent on the host system and site of occurrence of the disease and therefore may be problematic in patients with hematological disorders and recipients of Haematopoietic Stem Cell Therapy (Roden et al. 2005).

For antifungal treatment of mucormycosis, Amphotericin B deoxycholate (AmB) has been found to be the only licensed drug, however Liposomal AmB (LAmB) are found to be more effective with 71% success rate when used as salvage therapy for mucormycosis (Spellberg et al. 2009 and Walsh et al. 1998) and can be safely administered at higher doses for a longer period of time than AmB (Roden et al. 2005, Walsh et al. 1999). The 2016 recommendations from the European Conference on Infections in Leukemia (ECIL-6), as well as the ESCMID/ECMM guidelines, advocate the use of a lipid formulation of amphotericin B as first-line therapy for mucormycosis (Cornely et al. 2014 and Tissot et al. 2017).

Besides, the activity of anti-fungal drugs belonging to azole group like itraconazole is primarily restricted to Absidia species while fluconazole and voriconazole are not much reliable against the agents of mucormycosis (Trifilio et al. 2007 and Vigouroux et al. 2005). In contrast, in vitro experiments, posaconazole possesses enhanced activity against the Mucorales, with reported 90% minimum inhibitory concentrations (MIC90) of 1 to ≥ 4 μg/mL (Almyroudis et al.2007; Arikan et al. 2008 and Lass-Florl et al. 2008). Isavuconazole is a recently developed triazole, with a wide spectrum of antifungal activity including Mucorales(Rybak et al. 2015).

Nevertheless, posaconazole monotherapy cannot be approved as primary treatment of mucormycosis based on the available animal data and the absence of clinical data. In contrast, available clinical data from open-label salvage studies propose that posaconazole is practicable alternative for patients with mucormycosis who are intolerant to polyenes (van Burik et al. 2006 and Greenberg et al. 2006).Rhizopus oryzae belonging to family Mucoraceae expresses the target enzyme for echinocandins (Ibrahim et al. 2005) and in experimental conditions of DKA, mice infected with R. oryzae infection, treatment with combination of caspofungin plus Amphotericin BLipid Complex (ABLC) therapy markedly improved survival,compared with monotherapy (Spellberg et al. 2005a). Combination therapy of micafungin or anidulafungin with LAmB also improved the condition in neutropenic and DKA mice with disseminated mucormycosis (Spellburg et al. 2009). Immune stimulation resulted due to enhanced exposure of β-glucan on the surface of fungus, may be one of the mechanisms by which echinocandins enhances improvement of outcomes in mucormycosis (Lamaris et al. 2008).In a retrospective study, patients of rhino-orbital-cerebral mucormycosis along with diabetes, combination LFAB-caspofungin therapy was associated with significantly improved outcomes compared with polyene monotherapy (Reed et al. 2008).

Moreover, deferoxamine actually enhances delivery of iron to Mucorales, therefore, chelation therapy of deferoxamine iron predisposes to mucormycosis. As reported, animals infected with R. oryzae that are treated with iron or deferoxamine have markedly worse survival than do animalstreated with placebo. However, no other iron chelators can be used by Mucorales toacquire

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iron (Boelaert et al. 1993; Boelaert et al. 1994, Ibrahim et al. 2006 and de Locht et al. 1994).

However, in 2005, a new orally available iron chelator, deferasirox, was approvedby the US Food and Drug Administration for the treatment of iron overload among patientswith transfusion-dependent anemia (Cappellini, 2005). Deferasirox was fungicidal for clinical isolates ofMucorales in vitro, with an MIC90 of 6.25 µg/mL (Ibrahim et al. 2007). However, use of this drug can cause nausea and other side effects but they were usually mild and reversible upon cessation of drug use but there have been also rare postmarketing reports of severe acute renal failure resulting in hemodialysis or death in iron-overloaded patients receiving deferasirox (Spellburg et al. 2009).

Proinflammatory cytokines like interferon-γ and granulocyte macrophage colony Stimulating factor, enhance the ability of granulocytes to cause damage to the agents of mucormycosis (Gil-Lamaignere et al. 2005). Treatment with adjunctive immune therapy with recombinant granulocyte colony-stimulating factor and granulocyte macrophage colony-stimulating factor, or with recombinant interferon-γ, in conjunction with LFAB have described survival of patients with mucormycosis in certain case reports (Abzug et al. 2004; Ma et al. 2001 and Mastroianni et al. 2004).

II. CONCLUSIONS:

Mucormycosis is an emerging fungal infection and highly prevalent in immunocompromised patients, and the mortality with standard therapy remains unacceptably elevated. In the Indian context, the triad of diabetes (high genetic prevalence), unrestricted corticosteroid usage (increases blood glucose and fungal infection), and the ongoing COVID-19 appears to be the cause of the rise in mucormycosis (endothelia damage, lymphopenia, cytokine storm). Excessive usage of antibiotics (like azithromycin) and antifungal medications (like amphotericin B) during the Covid-19 pandemic may result in the emergence of resistance to these medications in the future (Sulis et al. 2021 and Pelfrene et al. 2021). Therefore, in order to prevent the emergence of such resistance, mucormycosis treatment should be regularly monitored.

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