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Review Article

Emergence of Mucormycosis: A Therapeutic Challenge for COVID-19 in Pakistan

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Abstract

Black fungus is opportunistic pathogens that may cause life-threating infection inimmunocompromised patients. The mucormycosis associated with COVID-19 is now become a serious health concern around the globe, including several Asian countries. In Pakistan mucormycosis fatalities are now being found among COVID-19 individuals. Individuals with diabetes, malnourishment, Cancer, organ transplantation, active tuberculosis, Liver diseases, chronic respiratory diseases, HIV, AIDS and asthma are more Susceptible to infection. Diabetes mellitus patients are at more risk of mortality infection of this fungus. To counteract mucromycosis in patients, rapid and precise diagnostic facilities, medical assistance, and a quick yet coordinated approach are all suggested.

Keywords: Black fungus, Immunocomprised patients, COVID-19.

INTRODUCTION

Meanwhile, as the world tries to deal with the devastation brought on by COVID-19, a new threat had also emerged: the "black fungus." There are 1,063,125 confirmed COVID-19 cases in Pakistan, with 23,797 fatalities, making it one of the severely affected countries by the pandemic [1]. Global epidemiological surveillance showed that mucormycosis infections are on the rise, especially high prevalence in Asian region [2]. Even before the COVID-19 pandemic, Pakistan have reported high incidence of mucormycosis infections approximately 14/100,000, despite the lack of sufficient information to determine the true burden of fungus illnesses in Pakistan [3]. Some mucormycosis fatalities are now being found among COVID-19 individuals at various hospitals in Pakistan, which is in line with the trend in Pakistan's neighboring nation, India [4].

Mucormycosis or Black fungus is an emerging and fatal fungal infection lead to severe infection in immunocomprised patients mostly related to diabetes mellitus. According to infectious site mucormycosis can be divided into six forms: pulmonary, rhino orbital cerebral, gastrointestinal, cutaneous and invasive infections. The phylum Glomeromycota includes opportunistic fungus such as cutaneous mucormycosis, which affects those with weakened immune systems [5]. More than 90% of people with COVID-19 associated mucromycosis (CAM) have diabetes, according to a research conducted worldwide (6). Immunocompromised persons, such as COVID-19 patients, diabetics, people taking steroids, and those with cancer and organ transplants, are more susceptible to infection (7). COVID-19 has been reported in several studies to link with significant mortality in diabetic ketoacidosis (DKA) patients, and these research indicated that DKA is a frequent and serious complication for patients with COVID-19 [8].

Not only can the virus damage the immune system of COVID-19 patients, but the treatment regimen utilized for severe cases (e.g. steroids) can also decrease their immunological reaction. COVID-19 patients hospitalized to critical care units getting oxygen therapy may come into contact with humidifiers in the ward, increasing their moisture exposure and so rendering them more vulnerable to a fungal infection. According to the International Diabetes Federation's figures, 8.9% of Indian adults are diabetic, totaling roughly 77 million people [9]. This review emphasize

the origin and occurrence of mucormycosis, its associated illnesses, its course in immunocompromised and COVID-19 afflicted patients, and the multiple risk factors and their impact on multiple organs, as well as the difficulties in overcoming this infection. As with the COVID-19 outbreak and increased pressure on healthcare system, this study will also provide a broad data foundation for optimum treatment results and prevention of this fungal infection.

Mucormycosis

Mucormycosis or zygomycosis is a deadly but occasional fungal disease caused by a mould's family known as mucormycetes. Mucormycosis, often known as "deadly black fungus" is a potentially fatal infection from the subphylum Mucoromycotina, order Mucorales [10, 11]. After Aspergillus, Mucorales are the most prevalent fungus discovered in haematological malignancies, solid organ transplantation and stem cell transplantation [12]. Mucormycosis is caused by 11 genus and 27 species of Mucorales [13]. Rhizopus is the most prevalent genus that causes mucormycosis, after Mucor and Lichtheimia. Mucorales may be found in a variety of environments, including soil, decayed food, dust and Manure [14].

Mucormycosis was firstly documented in 1855, when the first true human instance of the disease was discovered. Furbringer discovered pulmonary mucormycosis in 1876 in a cancer patient with a hemorrhagic infarct in right lung which was filled with fungus hyphae and spores in Germany. Mucormycosis was discovered in an autopsy in 1956. Mucormycosis is mostly transmitted by inhalation of fungal spores, the ingestion of contaminated food items and the infusion of fungus directly into skin abrasions or wounds [15].

Furthermore, outbreaks of mucormycosis might be nosocomial related to the contaminating ventilation systems, medical devices, hospital discards such as hospital clothes (linens), bandages and so on (16). Immunocompromised people are at most risk to be effected by mucormycosisas their immune systems are unable to combat the fungus. It is mostly identified by diagnostic examination of a biopsy taken from the infected site (17). According to infectious site mucormycosis can be divided into six forms: pulmonary, rhino-orbital cerebral, gastrointestinal, cutaneous and invasive infections. The phylum Glomeromycota includes opportunistic fungus such as cutaneous mucormycosis, which affects those with weakened immune systems. Among mucormycosis causing species.

Rhizopus cause ROCM. Meanwhile, Cunninghamellafound in two forms either pulmonary or disseminating and Saksenaea andApophysomyces were present incutaneous type.The most typical infection locations includes sinuses (39%), disseminated (23%); lungs (24%), and skin (19%) [18]. Initially the fungus invade the blood vessel causing thrombosis and tissue infarction. Angioinvasion occurs when fungal spores come into touch with endothelial cells. Moreinteractions with these cells' receptors leads to cell injury and proliferation of Fungus [19]. Fungi are often eliminated through polymorphonuclear phagocytes in healthy individuals. As a result, fungal growth is common in people who have defects in this process. Furthermore, Mucorales can be resistant to these processes, leaving them highly virulent [20].

Mucormycosis-associated Risk factor

Mucormycosis has been linked to a number of underlying factors that predispose a person to infection. COVID-19, diabetes, organ and stem cell transplantation, haematological diseases, trauma, burns, metabolic acidosis, steroidal usage, broad-spectrum antibiotics, malnutrition, Cancer, voriconazole use are some of these variables [21]. Figure 1 shows the association between COVID-19 and black fungus and several risk factors for onset of mucormycosis. Among the various types of mucormycosis infection, ROCM was linked to the existence of diabetes and cutaneou infections was more common in trauma patients, and in organ transplantation , pulmonary, intestinal, and disseminated types commonly found. Furthermore, haematological malignancies appeared in the disseminating form [22]. Mucormycosis is more common in people with diabetic ketoacidosis because of innate immunity in such people causes polymorphonuclear phagocytes to kill the fungus. The sinuses were the most afflicted area in diabetic individuals, following pulmonary areas [23].

During the neutropenia stage of the illness, those with haematological malignancies were prone to mucormycosis. Mucormycosis in haematological malignancies is caused by chemotherapy and use of voriconazole, which is used in aspergillosis treatment [24]. Mucormycosisfound more prevalent among peoplehaving acute leukaemia instead in those with someother kinds of cancer. The major modalities for prevention of mucormycosisamong individuals having haematological malignancies were avoiding exposures to environment, while therapeutic options included surgery, antifungal therapy, and neutropenia reversal. Soil as well as decaying organic matter such as leaves, rotten wood, compost piles, and animal feces are among the places where mucorales may be found. Because of the wide range of locations in which mucorales may be found, people are constantly being exposed to them. Basic hygiene measures can help protect against mucormycosis [25].

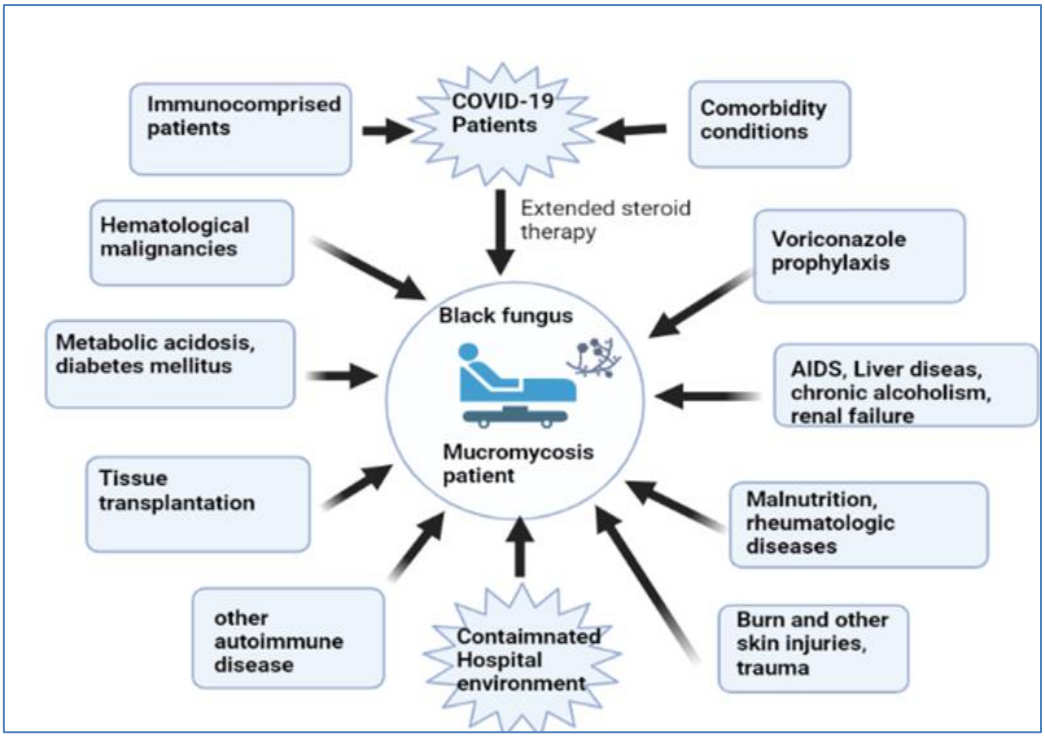

Fig-1: Association between COVID-19 and black fungus in contrast to several risk factors for onset of mucormycosis. Several risk factors that lead to the development of mucormycosis, includes comorbidity conditions, diabetes mellitus, and haematological malignancies HIV and other diseases, immunocompromised persons, voriconazole. Furthermore, immunosuppressive therapies such as stem cell therapy and organ transplantation render people more prone to the disease. Exposure of spores due to unhygienic Practices leads to mucromycosis.

Transplantation treatments have also been identified as one of the mucormycosis risk factors. However, the disease's occurrence varies depending on the type of organs donated. Because patients of transplantation treatments mostly given immune-suppressants and large dosage of steroids, they are most susceptible to the fungal infection. Furthermore, corticosteroids decrease macrophages and neutrophils, impairing the body's capacity to fight infection [26]. Individuals who use steroids are likewise considered at high-risk. Patients undergoing stem cell treatment are also given voriconazole, which, when administered prophylactically, reduces the incidence of mucormycosis [27].

Deferoxamine treatment and iron overload which is used for the treatment of people having diabetic ketoacidosis, renal failure with haemo-dialysis are at double risk of getting mucormycosis. However, deferoxamine treatment increases the risk of mucormycosis in individuals. The iron eliminated by the medication is utilised by the fungus to proliferate, creating a suitable environment for their development. Mucormycosis is not only seen in people with chronic illnesses; it may also be seen in those who have had surgery, most likely after utilizing contaminated goods (28). Because invasive mucormycosisbecomes more common in clinical settings, it is very critical to sustain a sterile, patient-safe atmosphere. Furthermore, caution should be exercised when aiding chronic patients. In therapeutic settings, circumstances are created to avoid the formation of mucormycosis.

Mucormycosis and COVID-19: a complicated relationship

COVID-19 has brought a slew of new diseases and difficulties around the globe [29].COVID-19 symptoms include an increase in body temperature, hypoxia, osmolarity and shortness of breath [30]. Recently, COVID-19 healed individuals have been troubled with a very new illness known as Mucormycosis disease. Mucormycosismay rapidly spread and invade the sinuses and lungs before moving on to the intra-orbital and cerebral spaces parts of the body. Complication of mucormycosis in COVID-19 infected person have been demonstrated in figure 2.The primary signs of COVID-19 offer an ideal setting for fungus to grow and flourish within the human body. Diabetics, people on systemic corticosteroids, patients of neutropenia, stem cell transplant, hematologic malignancies, and immune-compromised persons are all prone to mucormycosis [31]. Diabetes may enhance COVID-19 associated morbidity and mortality by the following mechanisms: i) decreased viral clearance, ii) reduction in T-cell activity, iii) increased cytokine storm iv) immuno-suppression [32]. In COVID-19 patients, hyperglycemia exacerbates the cytokine storm via disrupting endothelial cells, resulting in multi-organ destruction. The acidic environment and increased amounts of free ferric ions promote the development of

mucorales in diabetic ketoacidosis. These conditions favor the invasion and effective attachment of fungal hyphae inside the body. Persons with chronic diabetes who have foot ulcers are at risk for this infection because any damaged skin tissue is an accessible entrance point for this fungus. Furthermore, COVID-19 therapy is still in its early stages [33]. To counteract the effects of SARS-CoV-2 infection, patients are given high doses of steroids which decreases inflammation of the lungs and may help limit the damage done to the body by the cytokine storm. However, patients infected with this novel strain of COVID-19 are typically treated with high doses of steroids, as well as extensive use of oxygen masks with ventilators, which cause them more vulnerable to mucormycosis. Steroids lower both inflammatory response and immune response , where the synthesis of white blood cells (WBCs) as well as T-helper cells is reduced, allowing any foreign material to infiltrate and totally destroy the immune system inside the host cell. Furthermore, these hormones may cause an unregulated release of sugar, allowing themucorales to proliferate, reproduce, and invade at a rapid speed [34].

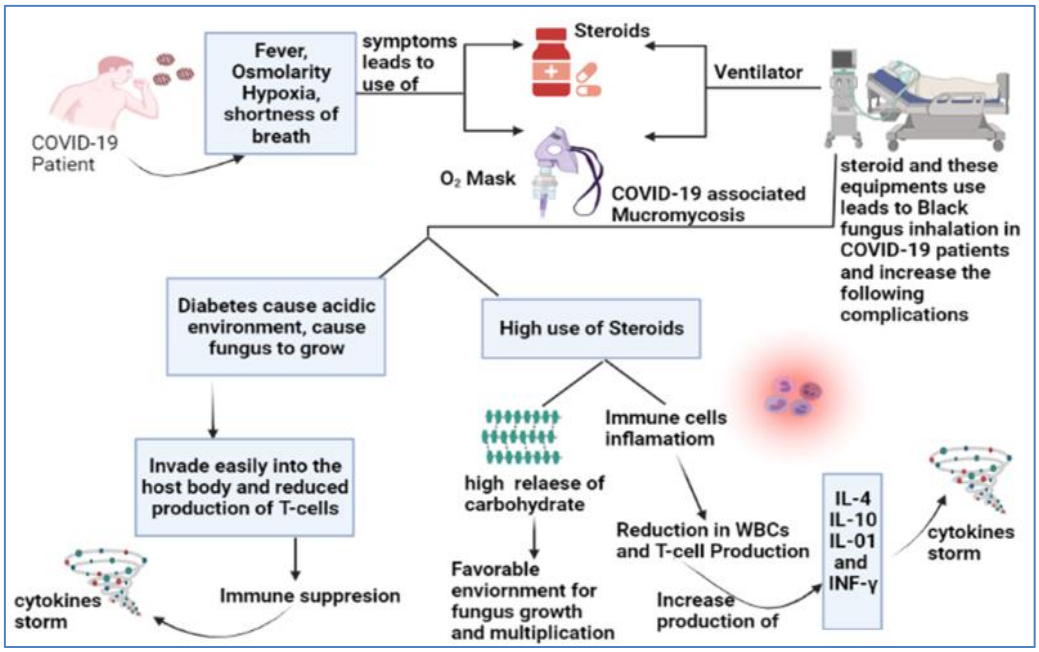

Fig-2

Figure 2: COVID-19 associated Mucormycosis (CAM): Because of dysregulation of immune system, a COVID-19-infected person is more susceptible to mucormycosis and may be given immune suppressant medications that inhibit the body's phagocytic cells from fighting the black fungus at an ideal level. COVID-19 additionally raises the level of iron in the blood, which the fungus requires to grow and multiply, making the patient more susceptible to infection. Persons infected with COVID-19 are frequently given oxygen treatment. Contamination in all these devices can act as a source of infection for mucormycosis. COVID-19 patients are at increased risk for this disease due to the steroid treatment they get.

COVID-19 associated Mucormycosis in Pakistan

An observational study have been conducted in a Hospital in Karachi, Pakistan on PCR confirmed COVID-19 cases of adult patients in July 2020 to May, 2021. Mucormycosis was identified by a combination of clinical, microbiologic, radiographic and histological examinations [35]. An old patient with a combination of diseases including diabetes, heart disease and hypertension was positive for COVID-19 have mucormycosis co-infection. He was treated with amphotericin B for fungal infection and broad-spectrum antibiotics for bacterial co-infections [36].

Severe COVID-19 infection also raise levels of pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α, while lowering the levels of CD4 INF-γ, CD4 and CD8 cells. This increases the risk of co-infection, including mucormycosis. The use of low-quality oxygen cylinders, a polluted and humid hospital environment, tap water in humidifiers, and an overuse of antibiotics can all contribute to the spread of mucormycosis infection [37]. According to a study in India, systemic corticosteroids were used to treat uncontrolled diabetes patients who also had rhino-orbital mucormycosis and were positive for COVID-19 [38]. An observational research conducted in Pakistan found a 15.6% fungus infection rate in patients with proven COVID-19 who needed ICU hospitalization [39]. Pakistan will face a significant challenge in prioritizing mucormycosis surveillance, prognosis, and management along with a rigorous COVID-19

infection. Combating cutaneous mucormycosis in underdeveloped nations is complicated by inadequate laboratory facilities and a lack of competence, making it difficult to keep reliable statistics of disease incidence [40].

CONCLUSION

In conclusion, COVID-19 potentially associated with an increased risk of subsequent bacterial and fungal infections, due to the result of immunologic dysregulation. In addition, the unregulated use of steroids, broad-spectrum antibiotics and monoclonal antibodies, as part of the COVID-19 treatment might lead to fungal illnesses or aggravate pre-existing fungal diseases. The increasing threat of deadly re-emerging infectious illnesses like mucormycosis, significantly risk public health security. An increase in mucormycosis infections has prompted a surge in demand for the antifungal medication like amphotericin B, the only recommended and effective therapy. Expanding laboratory testing capacity is critical in light of the COVID-19 pandemic. This will allow for better epidemiological surveillance, and awareness and preventative actions can help reduce the strain on our health care system. Importantly, early and accurate diagnostic facilities, as well as therapy and management of immunocompromised COVID-19 patients, should be developed to help and avoid CAM battle.

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