

“ASSOCIATION OF COVID WITH FUNGAL INFECTION”

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1. INTRODUCTION:

COVID-19 was declared a pandemic by the World Health Organization (WHO) in March 2020 because to its human-to-human transmission, which has affected more than five million people and resulted in more than half a billion deaths worldwide. There is injury to the alveolar with severe inflammatory exudation, in addition to lower acute respiratory syndrome. COVID-19 patients have lower levels of immunosuppressive CD4+ and CD8+ T cells, and the majority of ICU patients require mechanical ventilation, leading in a longer stay in the hospital. Patients with severe COVID-19 pneumonia and acute respiratory distress syndrome (ARDS) have developed fungal co-infections or invasive aspergillosis as a result of the prolonged ICU stay, the use of steroids, and immunomodulators.

COVID-19 patients develop what is known as mucormycosis, a black fungus infection that causes blindness, hearing loss, and death. In immune-compromised hosts, a fungus pathogen known as *Aspergillus* produces catastrophic disease. Due to the fungus's airborne nature, haematological malignancies are among the fungus's hosts, wreaking havoc on the lungs' frontline defences. Mucormycosis is a life-threatening infection that affects immunocompromised patients who have diabetic ketoacidosis, neutropenia, organ transplantation, and/or high serum iron levels. The number of individuals at risk for this lethal illness is rising as diabetes mellitus, cancer, and organ donation become more common. Despite aggressive therapy, which includes disfiguring surgical debridement and frequently adjunctive toxic antifungal therapy, the overall mortality rate is high. Severe viral pulmonary have risen and given birth to pulmonary aspergillosis (IPA). Most cases are IPA with 7-23% associated with fatality. This IPA is comparable to triple strain corona, which causes havoc in the lower respiratory tract and causes acute respiratory distress syndrome (ARDS). Patients in need of ICU have a high level of triple strain corona, which makes them more susceptible to mucormycosis. As a result, the fatality rate is expected to be significant. Mucormycosis is a fungal infection caused by fungus in the Mucorales order. *Rhizopus oryzae* is the most prevalent organism recovered from mucormycosis patients, accounting for 70 percent of all mucormycosis cases. Mucormycosis is caused by uncontrolled diabetes mellitus in ketoacidosis, various kinds of metabolic acidosis, corticosteroid medication, organ or bone marrow transplantation, neutropenia, trauma and burns, malignant hematologic diseases, and deferoxamine therapy in hemodialysis patients. The number of individuals at risk for this lethal illness is rapidly rising because of the rising prevalence of diabetes mellitus, cancer, and organ transplantation in the ageing US population. Despite disfiguring surgical debridement and adjunct antifungal therapy, the overall death rate for mucormycosis is still >50%, and it approaches 100% in individuals with widespread disease or chronic infection.

There have been studies which observed that this invasive aspergillosis has made up its mark in several parts of the world wherein it was found that 19 percent, 26 percent, and 33 percent of patients with severe COVID-19 pneumonia were from Netherlands, Germany, and France, respectively. Following an increase in COVID-19, an outbreak of Mucormycosis, popularly known as black fungus, is on the rise in India, which is already seeing a significant increase in COVID-19 cases. Face swelling, nasal congestion, Fever, cough, shortness of breath and headache are all symptoms of black fungus (mucormycosis). According to the Associated Press, more than 9,000 cases of the fungus have been reported. And the drug that can be used to treat it is running out. Because of the high number of patients infected with COVID-19, this potentially lethal fungal illness is likely to spread. People's immune systems may be impaired or weakened as a result of fighting the coronavirus, increasing their risk of developing mucormycosis.

New prevention and treatment techniques for mucormycosis are urgently needed. Understanding the pathogenesis of mucormycosis and the host's reaction to invading hyphae will eventually lead to new treatment targets. New ways to prevent and cure mucormycosis are clearly required, and such tactics can be aided by a thorough understanding of the disease's aetiology.

2. REVIEW OF LITERATURE

Mucormycosis, formerly known as zygomycosis, is a fungal disease caused by a variety of fungi in the Mucorales family. This family of fungi is commonly found in the environment (for example, in soil) and is generally associated with decaying organic matter like fruit and vegetables. *Rhizopus oryzae* is the member of this family that most commonly causes infection in people. However, another member of the Apophysomyces family, which thrives in tropical and subtropical climates, is also abundant in India. These fungi grow quickly in the lab and have a black/brown fuzzy look. Mucorales are opportunistic fungi, which means they infect people who have a weakened immune system or damaged tissue. Medicines that depress the immune system, such as corticosteroids, can damage immunological function, as can a range of other immunocompromising conditions, such as cancer or transplantation. Tissue damage can occur as a result of trauma or surgery.

We keep these omnipresent microorganisms at a distance and remain infection-free thanks to our bodies' defensive mechanisms, which are constantly and assiduously combating them. Once our immune system's defences are weakened, these germs gain the upper hand and unleash grotesque and often fatal infections. People with a weakened immune system are more prone to illness, as previously stated. Several reasons contribute to immune insufficiency, including:

- Diabetes: The combination of high blood sugar and an acidic environment, as seen in diabetic ketoacidosis, is ideal for rapid growth of these organisms. A weaker immune system is also linked to diabetes.
- Steroid medication raises blood sugar levels and lowers the body's immune response.
- Blood cancers, which result in a faulty immune system once again.
- Immunosuppressive patients, such as organ transplant recipients and haematologic stem cell recipients.
- Patients taking deferoxamine or who have an excess of iron (specifically used in iron overdose).
- Trauma, burns, and individuals who are underweight.

The disease isn't communicable and doesn't transmit from person to person. Mucormycosis can develop at any time after a COVID-19 infection, whether while in the hospital or several days to weeks after release. The medical treatment unwittingly boosts fungal growth by altering the host in a way that benefits the fungus. COVID-19 causes harm to both the mucosa of the airways and the blood vessels. It also boosts serum iron levels, which the fungus needs to thrive. Steroids, for example, raise blood sugar levels. Antibiotics that have a broad spectrum of action kill both harmful bacteria and healthy microbes. Aspergillosis is reduced by antifungals like Voriconazole, however Mucor is unaffected and thrives due to a lack of competition. Long-term ventilation lowers immunity, and humidifier water mixed with oxygen can spread the fungus. All of these factors combine to create an ideal setting for the spread of mucormycosis.

Nasal obstruction, haemorrhage, and discharge are all symptoms of mucormycosis. On endoscopic imaging of the nasal cavity, a distinct black eschar (slough or dead tissue) coated mass will be visible, suggesting the diagnosis. As the disease progresses, the palate may be injured, as demonstrated by a large black necrotic mass visible when the mouth is opened. When the orbit is involved, proptosis (eyeball protrusion), lack of eyeball motility, and consequent double vision ensue. There's a chance that one will get eye pain, redness, or even blindness. If the brain is invaded owing to blood artery obstruction, strokes, haemorrhages, and even death will occur. Patients may experience headaches, drowsiness, limb weakness, convulsions, and even death.

Fever, cough, and shortness of breath are symptoms of other fungal infections, such as Valley fever (coccidioidomycosis), histoplasmosis, and blastomycosis, which are comparable to COVID-19 and bacterial pneumonias. These fungi can only be found in dirt. People are infected by inhaling fungi that are present in the air. If COVID-19 testing is negative, clinicians should examine fungal pneumonias as a probable cause of respiratory disease. It's worth noting that these fungal infections can happen at the same time as COVID-19.

Based on clinical suspicion, an MRI and CT scan of the nasal cavity, sinuses, and brain are conducted. These provide a clear image of the existence and extent of the lesion. Clinical characteristics of lung mucormycosis are similar to COVID-19, including fever, cough, and shortness of breath, making clinical diagnosis challenging. When a patient is not improving or was improving but is now deteriorating for no apparent cause, a fungal infection should be considered. Additional lung abnormalities are revealed with a CT chest scan, which aids in diagnosis. The diagnosis is made by examining the bronchopulmonary lavage aspirate under a microscope.

Mucor hasn't wreaked havoc on Western countries as much as it has in India. COVID-19 patients have been observed to have a higher prevalence of fungal diseases like aspergillosis and candidiasis. Fungus-caused lung infections are difficult to diagnose clinically. Fever, cough, and shortness of breath are all indications of COVID in this patient. Diagnostic issues develop as a result of the overlap. When a COVID-19 patient appears to be improving but then has respiratory issues, the clinician should be on the watch for indicators of fungal

infection and have a low suspicion level. Bronchopulmonary lavage and fungus pathological investigation are essential to combine optimal treatment.

Rhino-orbital-cerebral-mucormycosis (ROCM) can be treated only when an endoscopic examination of the nasal cavity can confirm a fungal lesion if a clinical and radiological diagnosis has been obtained. Surgical debulking should be done right away. The procedure is intrusive and disfiguring, but given the existential threat of leaving any leftover tissue behind, it is justified. Any fungal or necrotic tissue should be removed from the entire nasal cavity. If the orbit is involved, surgery as invasive as exenteration of the eye socket's contents may be required. Surgical intervention should be carried out within a few hours following the diagnosis.

During treatment, careful use of steroids (to keep blood sugar levels in check), antibiotics, and other antifungal medicines is required. These infections are extremely deadly, and most people will die if they are not treated. The death rate varies between 25% and 90%. The danger of mortality is exceedingly great after the infection has spread to the brain. As a result, early detection and treatment are given a high priority. Mucormycosis is very harmful since it swiftly spreads throughout the body. The infection can spread to the lungs or the brain if left untreated. This can lead to:

- An infection of the brain
- Paralysis
- Pneumonia
- Seizures
- Death

Early diagnosis and therapy are critical for recovery from mucormycosis. It's possible that the infection will spread throughout the body. With this form of severe infection, death is a possibility. Because mucormycosis isn't communicable, one can't catch it from someone who has it. Self-care is the most effective strategy to avoid contracting this infection. It's critical to be safe outside if one has a weaker immune system. Preventing fungal infections can be as simple as wearing a mask while doing yard work and bandaging all wounds until they heal.

One should also take extra care during the summer and autumn months, when the amount of fungi in the environment is higher. Fever, headache, coughing, shortness of breath, bloody vomits, and changed mental status are all warning indications, as are pain and redness around the eyes or nose. According to the recommendation, mucormycetes infection should be considered if there is:

- Local pain on the cheek bone, one-sided facial pain, numbness or swelling
- Blackish darkening across bridge of nose/palate
- Loosening of teeth, jaw involvement
- Thrombosis, necrosis, skin lesion
- Chest pain, pleural effusion, worsening of respiratory symptoms

Antifungals can be used to treat mucormycosis, but it may eventually require surgery. According to experts, controlling diabetes, lowering steroid use, and stopping immunomodulating medications are all crucial. To maintain sufficient systemic hydration, the treatment includes an IV infusion of normal saline (IV), followed by an IV infusion of amphotericin B and antifungal medicine for at least 4-6 weeks.

Controlling hyperglycemia and monitoring blood glucose levels after Covid-19 treatment, as well as in diabetics, were stressed by experts on the task group. Steroids should be used with caution – the right time, dose, and duration are crucial. Microbiologists, internal medicine specialists, intensivist neurology, ENT specialists, ophthalmologists, dentists, maxillofacial/plastic surgeons, and others work together to treat Covid patients with mucormycosis.

Mucormycosis can result in the loss of the upper jaw and, in rare cases, the eye. Patients would have to accept the loss of function caused by a missing jaw, including trouble chewing, swallowing, facial aesthetics, and self-esteem, according to physicians. Whether it's the eye or the upper jaw, artificial alternatives or prostheses can be used to replace them. While prosthetic replacement of missing facial structures can begin once the patient has stabilised after surgery, doctors should reassure him about the availability of such interventions rather than leaving him to panic over the unexpected loss, aggravating a pre-existing post-Covid stress disorder. There is no link between receiving the vaccine and contracting a fungal illness. If one had a vaccine injection, one is more than likely to have a moderate COVID infection that doesn't require steroids, and one is less likely to get the black fungus.

Mucormycosis is the sole fungus that causes these diseases. People name it 'Black Fungus' when the fungus attacks the nose, face, orbits of the eyes, brain, and lungs, causing the tissues to turn black. When fungus infects the private areas, it produces a white discharge, hence the name white fungus. People now call it "yellow fungus" because of the yellow-colored pus that forms in the fungus-wounded area. Controlling the factors that cause these infections is more important than categorising these infections based on the colour of the discharge or the appearance of the body part. In most situations, it is the patient's elevated glucose level that puts them at danger of a fungal infection. Steroids are life savers in the current circumstances, amid the growing pandemic.

However, they must be used in small amounts for a short period of time. To the greatest extent possible, antibiotics should be avoided. COVID is a virus, not a bacterial infection. Antibacterial medications will only affect the healthy bacteria in the gut if they are used in COVID treatment.

3. CONCLUSION

Mucormycosis is an acute infection that has a significant impact on immunocompromised persons. Newly developed drugs have a variety of aetiology, but curing mucormycosis remains a difficult task. We're learning more about the unique and long-term manifestations of the Covid-19 infection. It has been identified as a potentially harmful link to invasive mucormycosis sinusitis, and it should be taken seriously. Two of the most prevalent causes of illness exacerbation are uncontrolled diabetes and excessive use of steroids, both of which must be addressed. Early surgical intervention and intravenous antifungal treatment should be considered in cases with post-coronavirus mucormycosis, as it can result in a better prognosis and a less fulminant illness course.

At first, the symptoms of mucormycosis may appear to be non-threatening. Patients and their carers must, however, recognise these symptoms early and receive the treatment needed to keep the situation under control. The most essential thing is that people speak with their doctors and follow up if they experience any of these symptoms. To learn more about the link between mucormycosis and Covid-19, more research has been done. Despite the fact that numerous treatments have reduced mortality, curing mucorales remains a challenge. Early diagnosis is time expensive and focuses on histological efficiency because the clinical presentation is nonspecific. Treatment can be started with direct culture inquiry, molecular diagnostic techniques, PCR, or in situ hybridisation. Mucormycosis is treated with antifungal injections, surgical intervention, and antifungal drugs given at the right time, depending on the underlying reasons. Immunologic and metabolic profiling are the best ways to approach this black fungus, mucormycosis. Nonetheless, one must remain vigilant, keep an eye out for any potential signs, and seek medical help as soon as possible. If detection and treatment are delayed, the consequences of this fungal infection could become even more deadly.

4. FUTURE ROADMAP

The discovery of important virulence factors' participation is a natural extension of the development of treatment strategies that will lead to interventional clinical trials. This type of clinical trial necessitates a substantial amount of time and effort in terms of study design, execution, and analysis. The potential benefits of therapies that complement current drugs for people with mucormycosis are significant. Patients with mucormycosis caused by COVID-19 should be diagnosed and treated as soon as feasible.

Clinicians should examine mucormycosis in patients with severe COVID-19, even if they don't have the traditional risk indicators for the disease. In individuals with mucormycosis, biomarkers for identifying invasive aspergillosis, such as beta-d-glucan and galactomannan, are frequently negative.

The aetiology of newly produced medications varies, however curing mucormycosis remains a difficult endeavour. We're learning more about the Covid-19 infection's unusual and long-term consequences. It has been recognised as a possible risk factor for invasive mucormycosis sinusitis and should be addressed seriously. Uncontrolled diabetes and excessive use of steroids are two of the most common causes of illness exacerbation, both of which must be addressed. In situations of post-coronavirus mucormycosis, early surgical intervention and intravenous antifungal treatment should be considered, as it can result in a better prognosis and a less fulminant illness course. Mucormycosis nowadays is commonly treated with antifungals such as amphotericin B, posaconazole, or isavuconazole, as well as vigorous surgical intervention but not with voriconazole.

Covid 19 is connected to a high prevalence of secondary infections, both bacterial and fungal, due to immunological instability. In addition, the use of long-acting steroids, monoclonal antibodies, and broad-spectrum antibiotics has resulted in the emergence or aggravation of pre-existing fungal infections. Physicians should be aware of the danger of such infections, especially in patients with risk factors, so that early detection and treatment can reduce death and morbidity. Therapeutic pharmaceutical use should be properly monitored, starting with the lowest dose for a limited duration. Antibiotics with a broad spectrum of action and monoclonal antibodies should be reconsidered.

Mucormycosis symptoms may appear to be non-threatening at first. It is vital, however, to diagnose and intervene as quickly as possible. Controlling blood sugar, removing dead tissue as quickly as feasible, and using antifungal drugs are all part of this. Improved awareness, better early detection tests, an emphasis on diabetes management and the cautious use of corticosteroids, timely surgery and antifungal therapy, and more research into prevention will be required to control these fungal infections.