REVIEW ARTICLE

Mucormycosis in Post-COVID Patients: A Review

Sabari Anand[1], Packia Sakaya Mercy[2], Manimekalai K[3], Bernaitis L[4], Benita Mary L[5]

Abstract

The mucormycetes fungus causes mucormycosis (also known as zygomycosis), a dangerous but uncommon fungal infection. Molds can be found in a variety of places. Mucormycosis is a fungus that primarily affects those who have health problems or who use medications that lower the body's ability to fight infections and sickness. It is a dangerous invasive fungal infection that can impact people who have uncontrolled diabetes, kidney failure, organ transplants, long-term steroid and immunosuppressive medicines, cirrhosis, burns, AIDS, and tumors such as lymphomas and leukemias. The researchers conducted a systematic review of a number of studies that demonstrated the presence of mucormycosis in post-COVID patients. The researchers began to observe how mucormycosis affected those who had been infected with a virus. We found nine articles on Google Scholar and the Internet using the keywords "COVID" and "mucormycosis," describing 13 post-COVID patients infected with mucormycosis. Mucormycosis can appear in at least six different clinical syndromes, including rhino-orbito-cerebral, lung, cutaneous, gastrointestinal, disseminated, and other: pulmonary disease (three study papers with four trials each and one research report with four patients); gastrointestinal disease (one research paper with one case); and disseminated disease (one research paper with one case). Seven of the 13 patients died, according to previous study reports. According to Worldometer, coronavirus disease-2019 (COVID-19) has been reported in almost 88 million cases, with nearly 1.9 million deaths globally. Despite the fact that there are no signs of mucormycosis in COVID patients, the death rate is over 50%. The situation is really alarming. Because delayed diagnosis and inadequate treatment can lead to poor outcomes, more research is needed.

Keywords: COVID-19, COVID-19-associated mucormycosis (CAM), Mucormycosis.

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Introduction

After candidiasis and aspergillosis, mucormycosis is the third most prevalent invasive fungal infection. Throughout this examination of Mucorales infections, the term "mucormycosis" is utilized. The Zygomycetes class is split into two orders: Mucorales and Entomophthorales. Mucorales are the causal agents of "Mucormycosis," a fulminant disease with significant morbidity and fatality rates that primarily affect patients with weakened immune systems. Species of the group Entomophthorales, on the contrary, are effective for significant subcutaneous illness in immune-competent people in tropical and subtropical locations. Metabolic acidosis (diabetic or anything else), iatrogenic immune suppressants, especially when associated with neutropenia and graft-versus-host disease in hematologic patients, use of glucocorticoids or deferoxamine, disruption of skin barriers by catheters and other equipment, and even exposure to infected bandages are all risk factors for the development of mucormycosis.[1] Due to revisions in taxonomy and nomenclature, the disease's etiological agents have been reclassified, and the condition has been appropriately named "mucormycosis."[2] In patients who acquire this condition, acidosis, uncontrolled diabetes, leukemia, lymphoma, AIDS, severe malnutrition, severe burns, cytotoxic therapy, and immunological suppression from corticosteroid use are all common predisposing factors. Patients with chronic renal failure, liver issues, and dialysis patients on deferoxamine medication have all been reported to have it. There are no documented age, racial, or sex-related predispositions. The majority of cases are surgical emergencies, although there have been a few cases of chronic, indolent forms manifesting with signs and symptoms over a 4-week period. The paranasal sinuses, lungs, skin, and gastrointestinal system are the most common invasion sites. Regardless of the etiology, mucormycosis has identical clinical symptoms, signs, and pathological findings.

[1–3]Department of Pharmacology, MGMCRI, Puducherry, India

[4]Department of Microbiology, Nandha Siddha Medical College and Hospital, Erode, Tamil Nadu, India

[5]Department of Physiology, Rajas Dental College and Hospital, Tirunelveli, Tamil Nadu, India

Corresponding Author: Sabari Anand, Department of Pharmacology, MGMCRI, Puducherry, India, Phone: +91 9489018018, e-mail: sabaria@mgmcri.ac.in

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These fungi have a tendency for invading arteries, resulting in massive emboli and tissue necrosis. Later in the infection's course, vein and lymphatic invasion may occur. Rhizopus thrives in the acidic, hyperglycemic environment that exists in persons with ketoacidotic diabetes mellitus. On the nasal and oral mucosal surfaces of diabetic and immunocompromised persons, there is thought to be a paucity of usual phagocytic activity. This permits fungus to multiply, which is not possible in people with normal phagocytic activity, and for the fungus to travel via blood vessels. In persons with ketoacidotic diabetes mellitus, the most common kind of rhinocerebral infection is found. This category is defined by sinusitis, face and eye pain, proptosis, and symptoms of orbital structural dysfunction. The nasal turbinates, septum, and sensation of taste all have necrotic tissue. This looks like a black eschar. As the fungus spreads through the ocular artery, the superior fissure, or the cribriform plate, intracranial involvement occurs.[3]

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Epidemiology

Rhizopus spp., *Mucor* spp., and *Lichtheimia* (earlier *Absidia* and *Mycocladus*) spp. are the most prominent mucormycosis agents. Rhizomucor, Saksenaea, Cunninghamella, and Apophysomyces are less common Mucorales genera. Mucormycosis can be induced by a number of different reasons in various countries. *Rhizopus* spp. (34%) were found to be the most frequently in mucormycosis patients in Europe, followed by *Mucor* spp. (19%) and *Lichtheimia* spp. (19%). While *Rhizopus* spp. constitute the most common cause of infection in India, new species such as *Apophysomyces elegans*, *A. variabilis*, and *Rhizopus homothallicus*, as well as atypical agents like *Mucor irregularis* and *Thamnostylum lucknowense*, are developing. Mucormycosis has become more widespread in recent decades as the number of persons who are severely immunocompromised has increased. Mucormycosis incidences have been reported from all around the world; however, epidemiological variations appear to exist between industrialized and poor countries. The condition is still uncommon in developed nations, and it is most typically observed in patients with hematological malignancies (HM). Mucormycosis is more prevalent in developing countries, especially in India; it is much more likely to strike those with uncontrolled diabetes or have been in a car accident.[4] As a result, mucormycosis prevalence is between 0.01 and 0.02 per lakh population in Europe and the United States, but it is significantly higher in India (14 per 100,000 population). Mucormycosis can manifest itself in a variety of ways, including rhino-orbito-cerebral, pulmonary, cutaneous, and disseminated types. In India, rhino-orbito-cerebral symptoms connected to uncontrolled diabetes were the most prevalent symptom, and isolated renal mucormycosis was discovered to be a separate clinical entity. Diabetes was shown to represent the underlying illness in 72% of patients in a large study of 418 cases in Mexico, and it was associated with sinusitis. Patients with underlying cancers had similar pulmonary and sinus manifestations.[5]

Disease Manifestation

Mucormycosis is a rarer fungus than opportunistic fungus such as Candida and Aspergillus. As per to one population-based study, mucormycosis affects about 500 persons in the United States each year, or 1.7 people per million (126). In a postmortem survey, mucormycosis was reported in 1–5 occurrences per 10,000 autopsies, making it 10- to 50-fold less prevalent than invasive Candida or Aspergillus infections (56, 154, 178). Finally, in patients at higher risk, such as those who have undergone allogeneic bone marrow transplantation, the prevalence of mucormycosis has been shown to be as high as 2–3% (90 and 96 in statistical). Based on clinical symptoms and anatomical location involvement, there are at least six clinical groups of mucormycosis: Irritable bowel syndrome is divided into four categories: pulmonary, cutaneous, gastrointestinal, disseminated, and miscellaneous. It is worth mentioning that invasive mucormycosis is more common in patients who have certain host defense deficiencies. In diabetic ketoacidosis, for example, the rhinocerebral variant of the disease is the most common, with pulmonary or disseminated disease occurring far less commonly. The mechanism behind ketoacidosis generating a preference for the rhinocerebral type of the disease is unknown. Because iron dissociates from isolating proteins in acidic conditions, people with metabolic acidosis or any other systemic acidosis have more available iron in their blood. However, disseminated disease is the most common sign of mucormycosis while taking deferoxamine, implying that increased accessible iron alone cannot explain the predominant frequency of rhinocerebral disease in ketoacidosis. While it has been discovered that hyperglycemia and acidity impact neutrophil chemotaxis and phagocytic activity, these findings do not explain why diabetic ketoacidosis patients are more likely to develop pulmonary mucormycosis rather than rhinocerebral disease. Mucormycosis is a major risk factor for myelodysplastic syndrome (perhaps due to iron overload from frequent blood transfusions) and steroid-treated graft-versus-host disease in transplant recipients. Despite the fact that less than half of patients are neutropenic at the time of illness onset, chronic neutropenia, hyperglycemia, and steroid use are all risk factors for mucormycosis in this situation. As stated further below, antifungal prophylaxis is increasingly being associated as a risk factor for mucormycosis. Prophylaxis with itraconazole or voriconazole has been linked to an increased risk of mucormycosis.

Rhinocerebral Mucormycosis

It is the most frequent kind of mucormycosis, with one-third to half of all cases. In diabetic patients in ketoacidosis, over 70% of rhinocerebral (also called as craniofacial) cases are seen. People who have had a solid organ transplant or who have had prolonged neutropenia have also been diagnosed with rhinocerebral mucormycosis. Rhinocerebral illness has recently become a more common complication in patients having hematopoietic stem cell transplantation. The majority of these cases have been correlated to the use of steroids to treat graft-versus-host disease. The initial signs are numbness and pain in the eyes or face of rhinocerebral mucormycosis, which are followed by conjunctival suffusion, photophobia, and soft tissue edema, which are similar to sinusitis or periorbital cellulitis. Fever is a symptom that can appear or disappear in half of the individuals. As long as the patient's bone marrow is functioning, white blood cell levels are normally elevated. Infection spreads from the ethmoid sinus to the orbit, leading proptosis and loss of extraocular muscle function if left untreated. Chemosis is also a possibility. It is possible that the virus will spread swiftly to surrounding tissues.[6]

Pathogenesis

Mucorales ingest or inhale spores, as well as inject spores into the skin, to assault deep tissues. A healthy host's initial line of defense, oxidative metabolites and cationic peptides, can kill spores as soon as they infiltrate lung or skin tissues. HIV, renal failure, organ or stem cell transplantation, iron overload, skin injury, broad-spectrum antibiotics, and intravenous drug usage, aspergillosis prevention with voriconazole, and malnutrition are all risk factors. Along with the clear increase in micronutrient availability and the body's weaker defense mechanisms, mucormycosis develops as a serious and often fatal illness in diabetics. (i) Rhizopus species have little serum inhibitory action, (ii) increased iron availability for the pathogen at lower pH levels, and (iii) rhizopus species have little serum inhibitory activity have all been proposed. Rhizopus has an enzyme called ketone reductase, which allows it to increase the level of sugar and acidity in its surrounding. Mucormycosis can develop in diabetic patients, especially those with ketoacidosis. The host's defense against mucorales is boosted by neutrophils. Diabetes mellitus inhibits the body's ability to function in a variety of ways. Ketoacidosis caused by diabetes hastens fungal invasion. Diabetics have a low level of dialyzable inhibitory factor, which, along with an acidic environment that allows more free iron to be released by lowering transferrin binding, is optimal for fungal

development. Mucormycosis had a reported fatality rate of 90% or more before the introduction of amphotericin B and extensive surgery. People who are severely neutropenic or have limited phagocytic activity are more likely to develop mucormycosis. In the case of HIV patients, however, this is not the case. It indicates that neutrophils, rather than T lymphocytes, are required to stop fungi from multiplying. After long-term voriconazole medication, patients with hematological malignancies and hematopoietic stem cell transplantation are more likely to develop mucormycosis. Mucormycosis can be found in people who do not seem to have any immunity issues. It is likely that it is linked to wounds, trauma, or iatrogenic elements in such cases.[7]

Laboratory Diagnosis

In all kinds of mucormycosis, neutrophils play an important role in the host's defense against mucorales. In DM, its function is disrupted at various levels. Diabetes-related ketoacidosis hastens fungal invasion. Diabetics with lower concentrations of dialyzable inhibitory factor release more free iron via reducing transferrin binding, allowing fungal replication to thrive. Mucormycosis had a reported fatality rate of 90% or greater before the introduction of amphotericin B and significant surgery. Mucormycosis is more prevalent in people who are severely neutropenic or have low phagocytic activity. That is not the case, however, with AIDS patients. It implies that neutrophils, instead of T lymphocytes, are essential in inhibiting fungal proliferation. After long-term voriconazole medication, patients with hematological malignancies and hematopoietic cell transplants are more likely to develop mucormycosis. Mucormycosis can also be found in patients who do not appear to have an immune system dysfunction. It may be linked to burns or trauma in such circumstances.[4]

Coronavirus disease-2019 (COVID-19) was detected in nasopharyngeal/oropharyngeal swabs using real-time polymerase chain reaction (RT-PCR) assay. To diagnose verified mucormycosis, histopathologic, cytopathologic, or direct microscopic inspection of fungus hyphae in biopsy specimens with concomitant tissue breakdown, or a positive culture result, was conducted. Possibility mucormycosis was defined as the existence of both host factors and clinical criteria with mycological evidence, whereas potential mucormycosis was defined as the presence of only host factor and clinical criterion criteria but no mycological criteria. Based on the clinical assessment, a deep nasal swab was sent for KOH mount and fungal culture. The disease was investigated using magnetic resonance imaging (MRI) of the orbit, brain, and paranasal sinuses, as well as computed tomography (CT). Systemic antifungals were started in conjunction between otorhinolaryngology and infectious disease specialists based on the initial nasal swab and radiographic result. While renal parameters were monitored, liposomal amphotericin B (5 mg/kg/day, up to 10 mg/kg/day for CNS infections; avoid gradual escalation) was delivered intravenously (IV).[6] The patient had endoscopic sinus debridement and biopsy, with the specimen sent to histology, microbiology for culture, and a sensitivity test. Based on the culture and histology findings, an oral antifungal, posaconazole, was begun (loading dose 300 mg twice a day on the first day, maintenance dose 300 mg orally once a day commencing on the second day). Orbital exenteration was conducted utilizing the eyelid-sparing method with transverse blepharorrhaphy in individuals who had an unsatisfactory response to systemic antifungals after 72 hours. After surgery, long-term oral antifungal medication was continued.[8]

Laboratory Findings

In patients with SARS, Middle East respiratory syndrome, and influenza, bacterial and fungal co-infections have been found; however, there is no evidence of co-infections, particularly fungal infections, in critically ill COVID-19 patients. As a result, medical practitioners dealing with the COVID-19 pandemic should be aware of COVID-19 patients with opportunistic fungal infections, as well as a list of risk factors, when treating COVID-19 patients.[1,3,9] Coronavirus disease-2019 (COVID-19) patients with ARDS who require a long stay in the intensive care unit (ICU) and ventilators, as well as those prescribed antibiotics for fungal infections like mucosal candidiasis, aspergillosis, mucormycosis, and *Pneumocystis jiroveci*, are common in people who take high doses of steroids, immunomodulators, interleukin antagonists, and broad-spectrum antibiotics, are common. The prevalence of COVID-19-related mucormycosis is unknown due to a lack of evidence (CAM). The most common sign of mucormycosis was rhino-orbital mucormycosis (ROM), which affected seven (47%) of COVID-19 patients, according to imaging, intraoperative endoscopic surveillance, and histological tests. SOM was detected in 33% of patients, with isolated ocular involvement in 13% and sinonasal mucormycosis in one case (7%). There was no evidence of pulmonary mucormycosis in any of the patients. Pansinusitis was the most frequent type of paranasal sinus infection. Mucormycosis had spread to the base of the skull in 10 (67%) of the cases. Pterygopalatine fossa involvement was found in 53.3% of individuals. In seven cases (46 %), cavernous sinus involvement developed.[10]

The white blood cell count was low, the C-reactive protein (CRP) level was high (35 mg/dL; upper limit norm 5 mg/dL), and the D-dimer level was within normal limits, according to medical data. A chest X-ray revealed bilateral basal coarse reticular opacities. Corona was found in a pharyngeal swab using RT-PCR. The patient, who had been admitted to the ICU, had continued to deteriorate and had hypoxemia (pO_2 46 mm Hg). Creatinine levels have increased, neutrophils were elevated (CRP was 140 mg/dL), white blood cells were elevated (12.75×10^9/L), interleukin-6 was high (365 ng/mL), and ferritin was rising (450 ng/mL), but lymphocytes were normal.[7] The patient was intubated and mechanically ventilated on his second day in the ICU. An X-ray of the chest revealed that the bilateral infiltrates had progressed, as well as pulmonary impairment. An endotracheal aspiration and a culture test were done during the patient's stay in the ICU. Voriconazole from *Aspergillus fumigatus* was developed in culture with fungal-like growth. Despite reacting to Aspergillus antigen, the lateral flow device was not colonized. Positive evidence of black fungus development was found in serum fungal markers. Fungal growth was detected using galactomannan and a 1,3-beta-D-glucan marker. The patient died on the fifth day in the ICU despite the fact that the fungal growth had been treated. Mucormycosis is a deadly disease that causes eyesight loss, hearing loss, severe heart attacks, and the destruction of brain cells. All seven individuals died, ranging in age and having mild-to-severe fungal infections. After a thorough search and study on mucormycosis yielded few or no results in terms of publications on this toxic fungus, one search result led to Yang et al., who discovered a slightly greater percentage of people with the condition. Antifungal medication was provided to several individuals; however, it was useless. A black fungus infection was detected in six out of 19 individuals in another German investigation associated with COVID-19. In the Netherlands, additional cases of black fungus infected with

A. fumigatus have been reported. Five patients in France were found to be infected with *Aspergillus flavus* after tracheal aspirates were cultured.

Many cases of COVID with fungal infection increased from 16 to 27% during that time span, with extremely ill patients dying. Since the start of this fungal outbreak, the majority of those with mucormycosis have died. Penicillin in mucormycosis is depicted in the diagram below. Antibiotics and other forms of diagnosis have slowed the spread of this fungus. This mucormycosis must be taken seriously in current COVID-19 patients.[9]

Discussion

Pulmonary mycormycosis has been described as a life-threatening fungal infection in a substantial number of clinical cases. Failure to diagnose early and precisely can potentially result in a catastrophic and chronic condition. The use of antifungal medicines is contingent on accurate and timely detection of fungal infection. A nasal cannula is required for a week during a chronic state of pulmonary mycormycosis. In this case study, the patient's condition is stable, but intubation is required. Because of the relationship between COVID-19 and lung disease, 125 mg of methylprednisolone was administered three times a week in 40 mg doses. The issue was satisfactorily managed with the usage of methylprednisolone. A patient was also weaned off of two support over time. The PICC line was stored in a clean, sterile environment. There were intermittent temperature spikes, and a blood culture collected from a PICC line showed the presence of pain-sensitive bacteria—*Klebsiella*. Imipenem, an antibiotic, was kept in use. The patient experienced hypokalemia and hypomagnesemia during the treatment, which were addressed. Creatinine levels also began to rise, peaking at 1.52 at one time. Hyponatremia was also present. The diabetes that was causing the problem was successfully managed. In comparison with the prior scan, a repeat PET CT revealed a partial metabolic response. The liposomal amphotericin B was discontinued after 6 weeks and substituted with oral posaconazole at discharge. After a month of oral posaconazole medication, the patient returned for a follow-up appointment.[11] In our series, the majority of the patients were men, which is consistent with other case studies from throughout the world. The most common underlying illness in our study was diabetes mellitus (DM). In the case of ketoacidosis, diabetes mellitus is associated with diminished neutrophil activity, microvascular insufficiency, and other metabolic abnormalities that enhance fungal development. *Rhizopus* species have a functional ketone reductase system, allowing them to live in high-glucose, acidic conditions. The glutathione system is also disrupted in these patients, resulting in diminished phagocytic activity. Rhizopus is inhibited by normal serum, while it is stimulated by the serum of diabetic ketoacidosis patients. In our study, four of the patients experienced diabetic ketoacidosis. Sixty-four percent of MCM patients had diabetes, and 55.6% had diabetic ketoacidosis, according to a study of 28 MCM patients. However, in other investigations, DM-related complications accounted for just 17% of MCM cases. Another factor that puts you at risk for MCM infection is chronic renal failure. Patients with hematological malignancies (mostly acute leukemia) had the highest prevalence and fastest-growing rates of MCM in the largest case series. In our investigation, six patients acquired hematological malignancies, all of which were acute leukemia (ALL and AML) (ALL and AML). Despite the fact that neutropenia has been established as an important determinant in the development of MCM, only two of our ALL patients had it. Fever, rhinorrhea, and headache were the most common signs and symptoms, with vision loss being the most serious.[12]

On a sample taken during debridement or a nasal swab taken during diagnostic nasal endoscopy, microbiological and radiological diagnosis as well as treatment performed, potassium hydroxide (KOH) wet mount, and fungal culture/sensitivity was performed. Mucormycosis was diagnosed microbiologically in six cases.[13] All of the patients tested positive for COVID-19 using reverse transcriptase polymerase chain reaction (RT-PCR). In our study, all of the individuals had diabetes. During their hospitalization, four patients developed diabetic ketoacidosis (DKA), and five more suffered DKA after starting corticosteroid therapy for COVID-19. For COVID-19 illness and mucormycosis, all patients in our study received intravenous dexamethasone and liposomal amphotericin B, according to the National Institute of Health. Four patients had remdesivir injections while in the hospital, and nine others required ventilator support. Steroids, monoclonal antibodies, and broad-spectrum antibiotics used to treat COVID-19 disease can raise the likelihood of a new onset or exacerbation of an existing fungal infection.[14] Dexamethasone was administered intravenously to all of the subjects in our study. The liposomal drug amphotericin B used for COVID-19 infection and mucormycosis four individuals died within a month of being diagnosed in our study, five had good systemic results but irreversible visual loss, and only one patient had adequate ocular and systemic outcomes. Infection with COVID-19 raises the likelihood of developing severe lung illness and interstitial pathology in the alveolo-interstitial area. If nothing more is done, you may be at risk of invasive fungal infections of the airways, such as the sinuses and lungs. Innate immunity is also altered as a result of COVID-19-related immunological dysregulation, as seen by a reduction in T lymphocytes, notably CD4 and CD8 cells. All physicians, including ophthalmologists, should be aware of the possibility of fungal infections like mucormycosis developing in COVID-19 patients in the future, especially those with comorbidities and who are on immunosuppressant therapy.[15]

Conclusion

The usage of glucocorticoids is most likely to blame for the development of mucormycosis, emphasizing that they should be taken with caution. Glucocorticoids should not be utilized in moderate COVID-19 cases (without hypoxia) or at higher glucocorticoid doses as a result. Medicines like tocilizumab, which target immune pathways, should be avoided unless there is a significant benefit. For improved outcomes, it is essential to diagnose and treat pulmonary mucormycosis as soon as possible.[14] New molecular biology technologies have been created in this regard to acquire an earlier diagnosis and begin appropriate medico-surgical treatment. In order to further optimize induction and consolidation treatment, comparative studies are required.[15]

Orcid

Packia Sakaya Mercy https://orcid.org/0000-0002-0761-1934
Bernaitis L https://orcid.org/0000-0003-0192-3467
Benita Mary L https://orcid.org/0000-0002-6490-9702

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