Review article

Mucormycosis in COVID 19 patients: A reviewSachidananda Mallya P.¹, Shrikara Mallya²¹Lecturer, Nitte (Deemed to be University), AB Shetty Memorial Institute of Dental Sciences (ABSMIDS), Department of Oral and Maxillofacial Pathology and Oral Microbiology, Mangalore, 575018, Karnataka, India² Professor, Department of Microbiology, AJ Institute of Medical Sciences and Research Centre, Mangalore, 575004, Karnataka, India

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Corresponding author: **Sachidananda Mallya P.** Email: mallyapsachin@gmail.com**ABSTRACT**

Our country is presently fighting against the second wave of Coronavirus and the medical professionals in India are not only worried about this fatal communicable virus but also other difficulties that are being declared by the patients. One such deadly problem being reported in patients in India in current times, who have produced positive result for COVID-19 and are slowly regaining health, is a fungal disease called mucormycosis or black fungus. With many such cases being announced in cities and states like Mumbai Bengaluru, Delhi, and Gujarat it has provoked an extra wave of fear among the general population. Mucormycosis, previously called as zygomycosis, is an uncommon fungal infection. It is caused by the mould related to mucorales, that is found mainly in decayed wood organic matters soil and leaves. They can cause blackening of skin, redness, inflammation, sores and can encroach the eyes, lungs and even the brain, substantiating to be dangerous if left without treatment. So, it is necessary to know the etiological factors and prominent symptoms associated with clinical implications of mucormycosis mainly invasiveness and perforation into deeper part of the bone. That is why it is necessary to identify immediately any possible bad signs of mucormycosis arising in both, COVID-19 patients, and other individuals. The report must be communicated to the healthcare workers without delay so that treatment can be provided at a suitable time and the patient recovers completely.

Keywords: COVID-19; mucorales; opportunistic; diabetic ketoacidosis; corticosteroid; angioinvasion.

INTRODUCTION

Mucormycosis is opportunistic local as well as systemic mycotic infection which occurs in several forms out of which acute and aggressive forms are uncommon and dangerous. Mucormycosis is caused by saprophytic fungi like *Rhizopus*, *Mucor*, *Cunninghamella*, *Rhizomucor* and rarely *Saksenaea*, *Apophysomyces*, or *Lichtheimia*.

Mucormycosis mainly attacks immunosuppressed patients, in persons with bone marrow-transplantation, hematological carcinomas, or uncontrolled diabetic persons (1). *Rhizopus* is the main pathogenic fungal organism which causes rhinocerebral mucormycosis. The species of *mucor* can grow on bread kept for weeks, in soil or on organic matter. *Mucor* may be isolated from swab collected from the oral cavity, nasal cavity, throat, and stools of healthy persons. Fungal spores germinate into hyphae in the human body after entering the tissues. Hyphae are responsible for the appearance of clinical symptoms, and persons with defective phagocytic function are at risk for developing an infection (2). Weakened phagocytic functions increase the speed of hyphal growth within the blood vessels, which results in ischemia, thrombosis, finally infarction and necrosis of tissues. In patients with diabetic ketoacidosis, the binding of iron to transferrin is inhibited which results in increased iron levels, which favors the growth of

mucormycosis (3). Six main clinical forms of mucormycosis are the rhinocerebral, pulmonary, cutaneous, gastrointestinal, central nervous system, and disseminated (4). Oral mucormycosis occurs usually in nasal areas or paranasal sinuses. Serious involvement of paranasal sinuses leads to necrosis of palate and/or ulceration (Fig.1;5,6).

R.D.Baker, an American pathologist named this member of zygomycosis as mucormycosis. It may be recognized as a rare fungal infection caused by *Mucorales* and *zygomycotic* species. The European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperation has identified diagnostic criteria for mucormycosis (7).

The official guidelines outlined by the Indian Council of Medical Research (ICMR) and the Ministry of Health and Family Welfare (MoHFW), for detecting symptoms and ensuring prompt diagnosis, efficient management of patients developing mucormycosis while recuperating from COVID-19 are as follows:

Most oral fungal lesions (oral mycosis) are opportunistic in nature. Oral fungal conditions vary from superficial to deep fungal infections of the oral tissues. The most diagnosed and reported oral fungal infections are the superficial candidiasis (oral thrush). Superficial fungal infections are usually associated with oral discomfort, pain, burning sensation, parageusia, and aversion to food (8). Deep fungal infections are characterized by the dissemination of

pathogens to the deeper part of the tissue and are usually associated with aggressive clinical presentation such as ulceration and perforation into bones. The specimens recommended for oral fungal lesions are the saliva, sample collected after rinsing oral cavity, scraping from the lesion and preparation of smear, moistened swab, impression smear, blister fluid, pus or exudate from the active lesion. The best method used for the oral fungal lesions that occur on the mucous membrane, lip, circumoral skin, and tongue is collection of material by using wet swab. A prosthodontic impression, swab, or smear is the best sampling methods in denture stomatitis cases.

Mucormycosis in humans can occur in distinct ways either superficial or localized like infection of skin, pinna of the ears, nails of fingers and systemic or disseminated like rhinocerebral, pulmonary and gastrointestinal forms. In these cases, spores may enter the body through the skin, the respiratory system or consumption of contaminated food. Rhinocerebral type comprises of 30 to 50% of

Fig. 1: Mucormycosis

Pathophysiology

An uncommon and severe complication of COVID-19 is mucormycosis. The predisposing factors for mucormycosis in Covid patients are diabetes mellitus with ketoacidosis, indiscriminate use of steroids and antibiotic or chemotherapy for cancer and individuals with transplantation of organs. The risk of mucormycosis is aggravated by simultaneous use of corticosteroids. The outcome can be improved by proper diagnosis and aggressive management. The pandemic coronavirus disease 2019 (COVID-19) continues to be a main problem worldwide. Even though there are several options for treatment to improve survival rate in COVID-19 only systemic glucocorticoid has found to be beneficial. Unfortunately, indiscriminate use of glucocorticoids can lead to secondary bacterial or fungal infections. Mucormycosis is unusually suspected or recognized in COVID-19 patient which has already claimed more than ten lakh lives through the world. Supportive care plays a major role in the management of COVID-19 as there is no effective antiviral therapy or vaccine. Drugs which are found to be beneficial in COVID-19 patients are

mucormycosis cases. The etiological agent was thought to be an emerging zygomycete *Apophysomyces elegans* (9). The infection can start in the paranasal sinuses resulting in necrosis of sinus and usually can spread to the sinuses, nasal cavity, and orbit before reaching brain. The symptoms are fever, blindness, abnormal protrusion of eye ball, bleeding per nose, paralysis or weakness of facial muscles, and signs and symptoms of invasion of trigeminal nerve. Rhino-sinus mucormycosis can lead to cavernous sinus thrombosis if not treated properly. Nasal turbinate and septum might become reddish black with characteristic postnasal drip (Fig. 2; 10). As the infection spreads into the cranial cavity, it causes lethargy, blindness, seizures and finally death. About 500 people every year die in the United States due to mucor infection (11). The infection due to candida or aspergillus are slightly lesser than mucor infection (12). Mucormycosis is likely to affect about 2% to 3% of allogenic bone marrow transplant recipients (13).

Fig. 2: Rhino orbito cerebral zygomycosis

glucocorticoids and probably remdesivir. Glucocorticoids are readily available cheap and have been demonstrated to reduce mortality in hypoxemic patients with COVID-19 (14). Nevertheless, glucocorticoids can increase the risk of secondary infections (15). Even though COVID-19 associated pulmonary aspergillosis (CAPA) has received much attention, mucormycosis, a devastating disease, remains unrecognized (16). The diagnosis of CAPA relies on the presence of risk factors, consistent radiology, and demonstration of aspergillus in tissue culture or microscopy (17).

The risk of infections in COVID-19 patients might be increased by impairment of physiological regulatory mechanism caused by the virus and the simultaneous use of immune modulatory drug like tocilizumab (18, 19). A important marker of invasive pulmonary aspergillosis is galactomannan in bronchoalveolar lavage but its role in CAPA has not been confirmed. Both invasive pulmonary aspergillosis and pulmonary mucormycosis have similar risk factors, clinical symptoms and signs, and radiological features. The diagnosis of CAM is thus even more difficult. The problem in clinical diagnosis and also

in isolation of the causative agent might contribute to the failure to recognize or correctly diagnose mucormycosis. Biomarkers which are useful in diagnosis of invasive aspergillosis such as beta-d-glucan and galactomannan are not available for mucormycosis. The patients with uncontrolled diabetes may have unnoticed or secret renal abnormality. Pulmonary mucormycosis is increasingly diagnosed, and the case fatality has improved overtime (20, 21). Control of hyperglycemia, early treatment with liposomal amphotericin B, and surgery are essential for the successful management of mucormycosis (22, 23). But the picture is entirely different in the management of COVID-19 where all three conditions of the management are negotiated.

1. The most commonly and effectively used drug in severe cases of COVID-19, that is glucocorticoids can aggravate blood glucose level.
2. Accompanying conditions such as ARDS and multi organ dysfunction might impede prompt diagnostic imaging and testing (24).
3. The fundamental services in hospitals like diagnostics and surgeries could be significantly deprived due to overwhelming response from Covid-19 patients.

So, the death rate in CAM (86.5% in the present series) maybe even much higher than in non-COVID patients (23). One fearsome observation was the lack of long-established risk factors, such as diabetes mellitus, hematological malignancies and transplantation in three cases with CAM. The indiscriminate use of glucocorticoids could be the cause for the development of mucormycosis and so this drug must be used judiciously. So, the glucocorticoids should not be used in mild cases of COVID-19 that is without hypoxemia or the use of large doses of glucocorticoids should be avoided. Further, if there is no clear-cut benefit of drugs suppressing immune pathways such as tocilizumab should be avoided (19).

Risk factors

Mucormycosis does not affect all covid-19 patients and those who take treatment for corona virus infection. The persons with the following predisposing factors are susceptible for opportunistic fungal infections.

1. Persons with uncontrolled diabetes mellitus especially with ketoacidosis
2. People having multiple medical conditions and those who are taking prolonged course of immunosuppressant drugs, indiscriminate use of steroid to treat previously existing diseases as well as present COVID19 infection.

3. The patients who have been treated in the intensive care unit of hospitals for a prolonged period.
4. In persons with preexisting diseases who have undergone organ transplant surgeries or on prolonged chemotherapy for cancer which resulted in suppressed immune system.
5. The persons who are already on antifungal agents for mycotic infection

In patients with altered innate immunity resulting from allogenic hematopoietic stem cell transplantation (HSCT), prolonged antimicrobial therapy, diabetes, indiscriminate use of steroids or immunosuppressive drugs, and stable organ transplantation (SOT; 24). The cases with traumas, major burns (25) or a few invasive medical procedures are also susceptible to mucormycosis.

The first case of Mucormycosis was reported in 1885 by Paltauf, a pathologist from Germany and coined it Mycosis Mucorina. Mucormycosis mainly affected immune compromised individuals during the decade from 1980 to 1990 (26). Based on a study did in France the incident rate showed a 7.4 percent increase every year. Mucorales enter the body either by inhalation or ingestion of spores or penetration of spores into the skin and then invade deeper tissues. These spores are destroyed as soon as they enter the lung or skin tissues by the primary line of defense through oxidative metabolites and cationic peptides. To summarize the risk factors for mucormycosis which include uncontrolled diabetes mellitus, particularly ketoacidosis, prolonged steroid use, extremes of age, neutropenia; especially with hematological malignancy, AIDS, renal insufficiency, organ or stem cell transplantation, excessive intake of iron, skin trauma, broad-spectrum antibiotics, intravenous drug misuse, prophylactic voriconazole for aspergillosis, and undernutrition (20) An adverse carping condition that can develop in diabetic individuals is mycotic infection mucormycosis, because of the elevated level of micronutrients and reduced defense mechanisms of the body (26), Various hypotheses include low serum inhibitory interest in *Rhizopus* species (ii) improved availability of iron for the pathogen at a lower PH level, and (iii) Diabetes mellitus patients' pulmonary macrophages have a diminished ability to suppress *Rhizopus* species germination (28). Ketone reductase is an enzyme present in *Rhizopus*. Because of the increased availability of micronutrients and the body's weakened defense mechanisms, enzyme that allows the organism to expand in a glucose and acidic environment. All types of mucormycosis can occur in diabetes mellitus, particularly with ketoacidosis. The important cells that take part in the host's defense mechanism against mucorales is neutrophils. In DM10 its function is impaired at a specific level. Diabetes-related ketoacidosis promotes

fungal invasion (29). The acidic environment loosens iron by lowering its binding to transferrin, and the presence of a dialyzable inhibitory component in diabetics provides ideal conditions for fungal duplication. Before the use of amphotericin B and radical surgery, the mortality rate for Mucormycosis was reported to be as high as 90% or higher (28). Mucormycosis is more common in severely neutropenic patients and those who lack phagocytic function. However, in the case of AIDS patients, this is no longer the case (28). It means that T lymphocytes aren't very good at inhibiting fungal proliferation, but neutrophils are. Patients with hematological malignancies and hematopoietic stem cell transplants are more vulnerable to mucormycosis when given voriconazole for an extended period of time (29). Mucormycosis can also be seen in people who don't seem to have a problem with their immune system (30). It may be linked to burns, trauma, or iatrogenic factors in such cases (31)

Symptoms of mucormycosis

The following symptoms and signs of mucormycosis should be kept in mind by medical doctor while treating COVID-19 patients with the above referred debilitated conditions.

1. Sinusitis, characterized by bloody or blackish discharge from nose with blocking of the nasal cavity
2. Pain on one side of the face, malar bones, with swelling and lack of sensation
3. Distinct blackish discoloration on the bridge of the nose
4. Striking pain in teeth, mandible, damaging of structures of tooth

Fig. 3: Mucor in LPCB mount

Histopathological features

The infected tissue shows wide putrefaction with various pale-staining, deep level aseptate hyphae with fanning at right points on examination. The growth in culture media might show round or oval sporangia. Hyphae are broad, hyaline, aseptate, irregular and collapsible that is ribbon like, ranging from 3 to 25 nm in width, spreading occasionally

5. Blurry or double vision, with objects appearing indistinct with pain in the eye
6. Abnormal clotting of blood with thrombosis of tissues, leading to damage or necrosis of skin or dermal cells
7. Worsening of respiratory functions, with chest pain, accumulation of fluid in lungs and hemoptysis.

Laboratory diagnosis

Mucormycosis have been reported with extension of lesions into facial tissue leading to perforation. The clinical diagnosis can be confirmed by microscopic examination of the tissue with a deeper connective tissue invasion, obtained by biopsy which reveals broad, aseptate hyphae with the hyphae branching at right angles (32). The structure of mucor can be confirmed by Grocott-Gomori methyamine silver stain which reveals broad irregular ribbon like collapsible aseptate hyphae (Fig-3). The fungal elements may be seen in marrow areas in cases with bony perforations during histopathological examination. The specimens collected from mucormycosis for histological diagnosis may show the absence of growth in fungal culture medium. It is necessary to do a thorough clinical examination of the oral cavity in invasive lesions to obtain a clinical diagnosis, since classical diagnostic methods which include imaging studies like radiographs, computerized tomography (CT), magnetic resonance (MR) culture studies (Fig-4), or serological tests may show negative results. Hence a good clinical study and histopathological examination remain the gold standard in diagnosis of mucormycosis (33).

Fig. 4: Growth of mucor on SDA

with protuberant hyphal growth. The picture in non-granulocytopenic disorder is entirely different. The necrotic tissue containing hyphae can be associated with signs of attack on blood vessels, localized necrosis with neutrophil invasion and granuloma formation. The staining methods used are Gomori's methamine silver or periodic Schiff stain. The method of analysis indicating mucormycosis includes detailed scrutiny of clinical symptoms, alluring

repercussion imaging modalities, early use of computed tomography (CT), expert evaluation of cytological and histological specimen, better use of clinical microbiological policy, and atomic detection. The finding of host conditions helps in the assessment of a patient's chances of developing invasive mucormycosis. The different methods used for detecting and classifying mucor species include PAS stains, calcofluor, histopathological assessment, Gomori's methenamine silver stain, culture, atomic strategies, and fluorescent in situ hybridization (34). According to Kontoyiannis (28), a significant issue in the identification of mucormycosis is its indescribable clinical appearance and mysterious circulation, necessitating the use of a sensitive nonculture-based informative methods that is tissue-based analysis. Other intense infections, such as carcinoma of maxillary sinus aspergillosis of maxillary sinus, delicate tissue radio rot, and other mucormycosis are differential findings (35).

Treatment

Quick specific conclusion, cautious debridement, and arrangement of medication, as well as adjunctive use of hyperbaric oxygen, recombinant cytokines, or granulocyte and prosthetic obturator bonding, are all effective treatments for mucormycosis. According to Spellberg (17), currently available monotherapy has a high death risk, especially in hematology patients, and thus the decision of "Mix care" for Mucormycosis has been proposed. Antifungal therapies include Amp B dexycholate, Liposomal Amp B (5-10 mg/kg), Amp B lipid complex, Amp B colloidal scattering, Posaconazole (400 mg bid), and center conditions supervision. Second-line therapy includes a combination of caspofungin and lipid Amp B, or a mixture of lipid Amp B and Posaconazole, but not Deferasirox. The diagnosis is based on the extent of the condition and the subsequent powerful treatment offered in response to the diseases.

Management of mucormycosis

The policies that are used in the management of mucormycosis cases includes both clinical and surgical strategies. The most used drug in the management of mucormycosis is liposomal amphotericin B, especially combination of liposomal amphotericin B and posaconazole showed synergistic effect. Combination management of liposomal amphotericin B and posaconazole showed synergistic effect against formation of fungal hyphae (19) in individuals with graft-versus-host disease. The oral posaconazole as prophylactic management against mucormycosis should be given to the patient with neutropenia, or individual with graft versus host reaction whereas mucormycosis cases in neutropenia or graft-versus-host disease patients should be given oral administration of fluconazole.

The specimen from aspergillosis cases shows septate hyphae that branch at 45° on microscopic examination. The other structures seen are conidiospores and fruiting bodies. It is also worth to note that hyphae of mucormycosis show non-septate hyphae that branch at 90° angle (15). Surgical management plays a significant role in treating invasive mucormycosis of sinus followed by local debridement with amphotericin B even though there are only few reports of local debridement. The management of invasive mucormycosis by systemic medication with amphotericin B (AMB), voriconazole, itraconazole, and caspofungin showed favorable response. A randomized clinical trial (RCT) study showed that voriconazole is more effective than deoxycholate amphotericin B (D-AMB) as a primary step in the management of invasive mucormycosis. Another RCT study on liposomal amphotericin B (L-AMB), showed that liposomal therapy can be used as alternative primary management strategy in few patients (14).

Prognosis and morbidity rate

The prognosis mainly depends on the course of the disease and following effective treatment and management. Survival rate depends on site of the infection: rhino cerebral mucormycosis 43%, focal cerebral mucormycosis 32%, pulmonary mucormycosis 30%, sinusitis without cerebral involvement 90%, cutaneous form 90%, disseminated infection 15%, and involvement of gastro intestinal tract 10%. Prognosis will be better in patients with low baseline serum concentration of iron / ferritin, neutropenia and malignant cases which is not associated with infection.

CONCLUSION

Physicians treating acutely ill COVID-19 patients must have knowledge of grave infections that can complicate the course of COVID-19. A high degree of clinical knowledge is necessary in case of pulmonary mucormycosis. Early diagnosis and timely management are required to improve the result in pulmonary mucormycosis. Mucormycosis is not a communicable disease. Some of the patient got through covid 19 infection but suffered from fatal secondary fungal infection due to risk factors such as weak immune system, diabetic ketoacidosis or persons with kidney transplant. The causative agents of mucormycosis are found on wet surface. When the Covid patient is put on oxygen support which has a humidifier containing water, the chances of them getting the fungal infection increase. The fungal disease is already known rare entity but the cases are increasing due to Covid-19 related complications where in the use of steroids raises the blood sugar level while some medicines result in suppression of immunity of patients. In such scenario the mucor infects the patient easily and spreads, if the fungus reaches the brain of the infected patient, it can prove

fatal. It can affect and destroy eye which might force the doctor to remove one of the eyes of a patient to save his life. The treatment should be started immediately with antifungal drug once the diagnosis of mucormycosis is confirmed. It must be taken either orally if the infection is still mild or administered via injections in more invasive cases. These effective drugs have the capacity to attack the fungal elements in the body and prevent their spread within the system, as well as totally curb their destructive activity. The efficacy of treatment of mucormycosis is increased by an accurate prompt diagnosis and giving immediate medical treatment by a panel of specialists. This reduces damage to various organs and completely blocks fungal infection thereby averting grave complications and fatal outcomes. It is advised to examine blood glucose levels even after the initial corona positive patient with diabetes mellitus shows negative result for COVID-19 and take medical care immediately if there is a sudden increase in blood sugar level. In situation where severe damage has occurred in tissues of the body, surgical treatment is required to remove this fungal growth. After receiving all necessary remedial measures, the physician keeps an observation on the patient, to ensure that mucormycosis does not recur and thereby guarantee effective treatment and total recovery of the patient. Additionally, simple preventive measures go a long way in lowering the chances of acquiring mucormycosis in post COVID-19 recovery, such as: Ensuring personal hygiene by bathing and scrubbing the body thoroughly, particularly after returning home from covid related work. Wearing face masks and face shields when going to dirty polluted environments such as construction sites. Making sure to wear fully covered clothing and concealed shoes, long pants, long-sleeved shirts, and gloves while coming in contact with soil, moss, manure, like in gardening activities. Another possibility of source of infection is contaminated nasal swab used for the collection of specimens for COVID test. So, it is necessary to inoculate atleast five nasal swabs from each batch in every hospital on Sabourauds Dextrose Agar (SDA) to rule out nasal swab as a fomite in transmission of mucor.

CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

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