An Overview about Mucormycosis and Correlation with Renal Functions

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Abstract

Background: Mucormycosis is an opportunistic fungal infection of the zygomycete family that can cause various types of infections. In most cases, there exist underlying conditions that predispose the hosts to the infection. As the fungi responsible are typical environmental organisms, they are usually non-pathologic in immunocompetent individuals. In immunosuppressed patients, however, these otherwise innocuous organisms can become a devastating and difficult-to-treat opportunistic infection. There are several clinical forms of infection: pulmonary, gastrointestinal, cutaneous, encephalic, and rhinocerebral. The latter must be differentiated from allergic fungal sinusitis, which is a non-invasive, local overgrowth in immunocompetent patients, Rarely, kidney may be involved by contiguous spread from overlying infected incision or from infected donor in renal transplant recipients. As the mucorales infections have an almost universal feature of extensive angioinvasion associated with thrombosis and ischemic necrosis, kidneys are similarly involved in the process with consequent complications. Some data have also demonstrated the ability of R. oryzae sporangiospores or hyphae to adhere to subenthodelial matrix proteins and human endothelial cells. The clinical manifestations of renal mucormycosis depend upon whether the disease is unilateral or bilateral and whether it is disseminated or isolated to the kidney. The common clinico-laboratory features in this condition described by researchers, were fever (88%), flank pain and tenderness (70%), haematuria and pyuria (70%), and concomitant bacterial urinary tract infection (53%). Acute renal failure was observed in 92% of patients with bilateral renal involvement. As emphasized by these authors, mucormycosis is being increasingly encountered as a cause of otherwise unexplained acute renal failure. Prognosis of renal mucormycosis is dismal with nearly 100% mortality in patients with bilateral renal involvement and acute kidney injury. Majority of survivors of renal mucormycosis have been those with unilateral renal involvement who received timely appropriate antifungal therapy with nephrectomy

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Mucormycosis is an opportunistic fungal infection of the zygomycete family that can cause various types of infections. In most cases, there exist underlying conditions that predispose the hosts to the infection. As the fungi responsible are typical environmental organisms, they are usually non-pathologic in immunocompetent individuals. In immunosuppressed patients, however, these otherwise innocuous organisms can become a devastating and difficult-to-treat opportunistic infection.There are several clinical forms of infection: pulmonary, gastrointestinal, cutaneous, encephalic, and rhinocerebral. The latter must be differentiated from allergic fungal sinusitis, which is a non-invasive, local overgrowth in immunocompetent patients **(1).**

Mucormycosis is characterized by tissue necrosis due to an invasion of blood vessels and subsequent thrombosis, which usually follows a rapid progression. The key to treatment is early and aggressive surgical debridement, along with high doses of intravenous antifungal therapy **(2).**

Etiology

Mucormycosis is an infectious disease caused by a fungus of the class of Zygomycetes and the order of Mucorales. The species most frequently isolated from patients are Apophysomyces (A. variabilis), Cunninghamella (C. bertholletiae), Lichtheimia [Absidia] (L. corymbifera L. raosa), Mucor (M. circinelloides), Rhizopus (R. arrhizus (oryzae) R. microsporus), Rhizomucor (R. pusillus), and Saksenaea (S. vasiformis) **(1).**

In patients with overt immunocompromise (i.e., transplant patients, HIV, patients of chronic steroids or disease-modifying anti-rheumatic medications, leukemia or other cancer patients), they can present with rapidly progressive necrotizing infection. Similarly, uncontrolled diabetics (particularly those with a history of diabetic ketoacidosis) are also at risk **(3).**

Epidemiology

Mucorales are thermotolerant fungi found in soil and decaying matter and rarely cause disease because of low virulence. Rhizopus is considered the most frequent fungal infection in immunocompromised populations, though various Aspergillus species are also commonly encountered **(2).**

Mucormycosis has increased its frequency because of the increased prevalence of immunosuppression states in the general population owing to improved lifespan in cancer and transplant patients, as well as expanding indications for immunosuppressive medications for various autoimmune diseases **(4).**

Signs and symptoms

Signs and symptoms of mucormycosis depend on the location in the body of the infection. Infection usually begins in the mouth or nose and enters the central nervous system via the eyes. If the fungal infection begins in the nose or sinus and extends to brain, symptoms and signs may include one-sided eye pain or headache, and may be accompanied by pain in the face, numbness, fever, loss of smell, a blocked nose or runny nose. The person may appear to have sinusitis. The face may look swollen on one side, with rapidly progressing "black lesions" across the nose or upper inside of mouth. One eye may look swollen and bulging, and vision may be blurred **(5).**

Fever, cough, chest pain, and difficulty breathing, or coughing up blood, can occur when the lungs are involved. A stomach ache, nausea, vomiting and bleeding can occur when the gastrointestinal tract is involved. Affected skin may appear as a dusky reddish tender patch with a darkening centre due to tissue death. There may be an ulcer, and it can be very painful. Invasion of the blood vessels can result in thrombosis and subsequent death of surrounding tissue due to a loss of blood supply. Widespread (disseminated) mucormycosis typically occurs in people who are already sick from other medical conditions, so it can be difficult to know which symptoms are related to mucormycosis. People with disseminated infection in the brain can develop changes in mental status or lapse into a coma **(6).**

Mechanism

Most people are frequently exposed to Mucorales without developing the disease. Mucormycosis is generally spread by breathing in, eating food contaminated by, or getting spores of molds of the Mucorales type in an open wound. It is not transmitted between people.The precise mechanism by which diabetics become susceptible is unclear. *In vivo*, a high sugar level alone does not permit the growth of the fungus, but acidosis alone does. People with high sugar levels frequently have high iron levels, also known to be a risk factor for developing mucormycosis. In people taking deferoxamine, the iron removed is captured by siderophores on *Rhizopus* species, which then use the iron to grow **(7).**

Diagnosis

There is no blood test that can confirm the diagnosis. Diagnosis requires identifying the mold in the affected tissue by biopsy and confirming it with

a fungal culture. Because the causative fungi occur all around and may therefore contaminate cultures underway, a culture alone is not decisive **(8).**

Tests may also include culture and direct detection of the fungus in lung fluid, blood, serum, plasma and urine. Blood tests include a complete blood count to look specifically for neutropenia. Other blood tests include iron levels, blood glucose, bicarbonate, and electrolytes. Endoscopic examination of the nasal passages may be needed **(9).**

Imaging

Imaging is often performed, such as computed tomography (CT) scan of lungs and sinuses. Signs on chest CT scans, such as nodules, cavities, halo signs, pleural effusion and wedge-shaped shadows, showing invasion of blood vessels, may suggest a fungal infection, but do not confirm mucormycosis. A reverse halo sign in a person with a blood cancer and low neutrophil count is highly suggestive of mucormycosis **(10).**

CT scan images of mucormycosis can be useful to distinguish mucormycosis of the orbit and cellulitis of the orbit, but images may appear identical to those of aspergillosis. Magnetic resonance imaging (MRI) may also be useful. Currently MRI with gadolinium contrast is the investigation of choice in rhinoorbito-cerebral mucormycosis **(11).**

Culture and biopsy

To confirm the diagnosis, biopsy samples can be cultured. Culture from biopsy samples does not always give a result as the organism is very fragile. To precisely identify the species requires an expert. The appearance of the fungus under the microscope will determine the genus and species. The appearances can vary but generally show wide, ribbon-like filaments that generally do not have septa and that—unlike in aspergillosis—branch at right angles, resembling antlers of a moose, which may be seen to be invading blood vessels **(12).**

Pathophysiology

Mucorales are present in soil and decaying matter, in immunocompetent people, the spores of Mucorales that reach the respiratory tract adhere to the nasal mucus and are eliminated either by swallowing or sneezing, if there is any wound in the mucous membranes, the polymorphonuclear neutrophils phagocytose and destroy the fungal structures. Neutrophils are the host defense against these infections; therefore, individuals with neutropenia or neutrophil dysfunction are at the highest risk. This is seen clinically in leukemia patients and bone marrow transplant patients, who are at the highest risk **(13).**

Rhizopus arrhizus studies have demonstrated that the ketone bodies present in these patients are metabolized by a ketone reductase, which allows them to survive in conditions with an acid medium; thus, the fungi become hyphal forms in host tissues and then invade blood vessels.

This angioinvasion results in vessel thrombosis and tissue necrosis **(14).**

Diabetes patients usually present with clinically uncontrolled diabetes and the increased amounts of circulating glucose, providing excellent conditions for the rapid development of filamentous structures that first bind to blood vessels and then penetrate them, completely clogging them in a few days and causing extensive areas of ischemic necrosis. Also, metabolic acidosis prevents chemotaxis of polymorphonuclear leukocytes, causes decreased phagocytic activity, and reduces local inflammatory response in a patient whose immune system is already compromised from one or more additional diseases **(15).**

Evaluation

Routine blood work is rarely diagnostic but can find the presence of neutropenia as a correlating risk factor. Imaging can be valuable in evaluating the extent of the disease. Radiological imaging studies are required to investigate areas with suspected mucormycosis, specifically in the brain, paranasal sinuses, lungs, and abdomen, always guided by the clinic **(16).**

The first intervention in the suspicion of rhinocerebral mucormycosis is with the endoscopic evaluation and biopsy of the sinuses to examine for tissue necrosis and to obtain examples of tissue, the presence of characteristic hyphae provides a presumptive diagnosis. The area of highest-yield, and greatest accuracy, is to biopsy the middle turbinate. CT scan can help evaluate contiguous structures such as the eyes and brain,

findings in CT scan included soft tissue edema of cavity mucosa, sinus mucoperiosteal thickening, bone erosions, and orbital invasions **(17).**

Patients with immunosuppression and respiratory symptoms should have a CT chest for possible pulmonary mucormycosis. The presentation of the infection does not differ from pneumonia; therefore, the diagnosis is difficult. Chest radiologic findings are pleural effusion, nodules, consolidation, and ground-glass infiltrates. Bronchoalveolar lavage can show broad nonseptate hyphae. If there is a concern for gastrointestinal mucormycosis (abdominal pain, gastrointestinal bleeding), a CT scan to evaluate for colitis is necessary. Once confirmed, colitis should be further investigated by endoscopy with biopsy. The presence of characteristic hyphae in the biopsy provides a presumptive diagnosis **(18).**

CLINICAL MANIFESTATIONS

The clinical hallmark of invasive mucormycosis is tissue necrosis resulting from angioinvasion and subsequent thrombosis. In most cases, the infection is rapidly progressive and results in death unless underlying risk factors (ie, metabolic acidosis) are corrected and aggressive treatment with antifungal agents and surgical excision is instituted **(19).**

Based on its clinical presentation and anatomic site, invasive mucormycosis is classified as one of the following 6 major clinical forms: (1) rhino-orbitocerebral, (2) pulmonary, (3) cutaneous, (4) gastrointestinal, (5) disseminated, and (6) uncommon rare forms, such as endocarditis, osteomyelitis, peritonitis, and renal infection. Any of the species of the Mucorales may cause infection at these sites **(20).**

The most common reported sites of invasive mucormycosis have been the sinuses (39%), lungs (24%), and skin (19%). Dissemination developed in 23% of these cases. The overall mortality rate for the disease is 44% in diabetics, 35% in patients with no underlying conditions, and 66% in patients with malignancies. The mortality rate varied with the site of infection and host: 96% of patients with disseminated infections, 85% with gastrointestinal infections, and 76% with pulmonary infections died. In children, mucormycosis manifested as cutaneous, gastrointestinal, rhinocerebral, and pulmonary infections in 27%, 21%, 18% and 16% of cases, respectively, in one study. The skin and gut are affected more frequently in children than in adults **(21).**

Pulmonary Mucormycosis

Pulmonary mucormycosis occurs most often in neutropenic patients with cancer undergoing induction chemotherapy and those who have undergone hematopoietic stem cell transplantation (HSCT) and have graft-versus-host disease. The overall mortality rate in patients with pulmonary mucormycosis is high (76%); it is even higher in severely immunosuppressed patients. The clinical features of pulmonary mucormycosis are nonspecific and cannot be easily distinguished from those of pulmonary aspergillosis. Patients usually present with prolonged high-grade fever (>38°C) that is unresponsive to broad-spectrum antibiotics. Nonproductive cough is a common symptom, whereas hemoptysis, pleuritic chest pain, and dyspnea are less common **(22).**

In rare circumstances, pulmonary mucormycosis can present as an endobronchial or tracheal lesion, especially in diabetics. Endobronchial mucormycosis can cause airway obstruction, resulting in lung collapse, and can lead to invasion of hilar blood vessels with subsequent massive hemoptysis. Pulmonary mucormycosis may invade lung-adjacent organs, such as the mediastinum, pericardium, and chest wall **(23).**

The signs of pulmonary mucormycosis on chest images are also nonspecific and indistinguishable from those of pulmonary aspergillosis. The most frequent findings include infiltration, consolidation, nodules, cavitations, atelectasis,

effusion, posterior tracheal band thickening, hilar or mediastinal lymphadenopathy, and even normal findings. The air crescent sign may be observed and is similar to that seen with pulmonary aspergillosis.

In a study of CT scan features in 45 patients with haim munk syndrome (HMs) who had pulmonary mucormycosis or invasive pulmonary aspergillosis, researchers found that the presence of multiple lung nodules (≥10) and pleural effusion on initial CT scans was an independent predictor of pulmonary mucormycosis. Researchers have observed that the CT finding of a reversed halo sign, a focal round area of

ground-glass attenuation surrounded by a ring of consolidation, is more common in patients with mucormycosis than in those with other invasive pulmonary fungal infections **(24).**

Rhinoorbito-cerebral Mucormycosis

ROCM is the most common form of mucormycosis in patients with diabetes mellitus. It may also occur in patients with underlying malignancies, recipients of hematopoietic stem cell or solid organ transplants, and individuals with other risk factors **(2).**

The infection develops after inhalation of fungal sporangiospores into the paranasal sinuses. The infection may then rapidly extend into adjacent tissues. Upon germination, the invading fungus may spread inferiorly to invade the palate, posteriorly to invade the sphenoid sinus, laterally into the cavernous sinus to involve the orbits, or cranially to invade the brain**.** The fungus invades the cranium through either the orbital apex or cribriform plate of the ethmoid bone and ultimately kills the host. Occasionally, cerebral vascular invasion can lead to hematogenous dissemination of the infection with or without development of mycotic aneurysms. The initial symptoms of ROCM are consistent with those of sinusitis and periorbital cellulitis and include eye and/or facial pain and facial numbness followed by blurry vision. Signs and symptoms that suggest mucormycosis in susceptible individuals include multiple cranial nerve palsies, unilateral periorbital facial pain, orbital inflammation, eyelid edema, blepharoptosis, proptosis, acute ocular motility changes, internal or external ophthalmoplegia, headache, and acute vision loss **(25).**

Cutaneous Mucormycosis

Cutaneous mucormycosis results from direct inoculation of fungal spores in the skin, which may lead to disseminated disease. The reverse (dissemination from internal organs to the skin) is very rare. Researchers noted such reverse dissemination in only 6 cases (3%). Depending on the extent of the infection, cutaneous mucormycosis is classified as localized when it affects only the skin or subcutaneous tissue; deep extension when it invades muscle, tendons, or bone; and disseminated when it involves other noncontiguous organs **(26).**

The clinical manifestations of cutaneous mucormycosis vary. Its onset may be gradual, and it may progress slowly, or it may be fulminant, leading to gangrene and hematogenous dissemination. The typical presentation of cutaneous mucormycosis is a necrotic eschar accompanied by surrounding erythema and induration. However, a nonspecific erythematous macule, although small and apparently insignificant, may be the cutaneous manifestation of disseminated disease in an immunosuppressed patient. Authors have reported other, less common presentations of cutaneous mucormycosis, such as superficial lesions with only slightly elevated circinate and squamous borders resembling tinea corporis, targetoid plaques with outer erythematous rims and ecchymotic or blackened necrotic centers, and, in patients with open wounds, lesions with a cottonlike appearance resembling that of bread mold. When cutaneous mucormycosis presents with necrotic eschars, these lesions may mimic pyoderma gangrenosum, bacterial synergistic gangrene, or other infections produced by bacteria or fungi **(27).**

Gastrointestinal Mucormycosis

Gastrointestinal mucormycosis is uncommon and seldom diagnosed in living patients. In such cases, diagnosis is delayed, and the mortality rate is as high as 85%. Only 25% of gastrointestinal mucormycosis cases are diagnosed antemortem, and authors have reported the disease mainly in premature neonates, malnourished children, and individuals with haim munk syndrome (HMs), diabetes mellitus, or a history of corticosteroid use. Gastrointestinal mucormycosis is acquired by ingestion of pathogens in foods such as fermented milk and dried bread products. Consumption of fermented porridges and alcoholic drinks derived from corn may promote gastric mucormycosis. Use of spore-contaminated herbal and homeopathic remedies is also linked with gastrointestinal mucormycosis **(27).**

Disseminated Mucormycosis

Mucormycosis in one organ can spread hematogenously to other organs. The organ most commonly associated with dissemination is the lung. Dissemination also occurs from the alimentary tract, burns, and extensive cutaneous lesions. Although the brain is a common site of spread, metastatic lesions may also be found in the liver, spleen, heart, and other organs **(28).**

Uncommon Forms of Mucormycosis

Other less common or unusual focal forms of mucormycosis include endocarditis, osteomyelitis, peritonitis, and pyelonephritis. Specifically, mucormycosis is a rare cause of prosthetic or native valve endocarditis. Intravenous drug use is the typical risk factor. Endocarditis occurs principally on or around prosthetic valves and can cause aortic thrombosis **(29).**

Osteomyelitis usually occurs after traumatic inoculation or surgical intervention (eg, tibial pin placement, anterior cruciate ligament repair). Authors have reported osteomyelitis of the tibia, cuboid, calcaneus, femur, humerus, scapula, metacarpals, phalanges, and sternum. Hematogenous osteomyelitis is extremely rare. Also rare is involvement of the peritoneal cavity by Zygomycetes in patients undergoing continuous ambulatory peritoneal dialysis **(30).**

Although rare, renal mucormycosis should be suspected in any immunocompromised patient who presents with hematuria, flank pain, and unexplained anuric renal failure. Isolated renal mucormycosis has occurred in intravenous drug users as well as renal transplant recipients in developing countries with warm climates such as India, Egypt, Saudi Arabia, Kuwait, and Singapore. Another rare manifestation of mucormycosis is brain involvement (typically in the basal ganglia) without rhino-orbital involvement in patients with leukemia and intravenous drug abusers. Finally, isolated mucormycosis in the mastoid, oral mucosa, bone, the bladder, the trachea, the mediastinum, or the ear is rare **(31).**

Treatment / Management

The standard management of mucormycosis requires early diagnosis, a reversal of risk factors and underlying illness, surgical debridement, and prompt administration of intravenous antifungals - usually amphotericin B. This entails the prompt management of hyperglycemia, acidosis, and cessation of immunosuppressive agents when possible. Surgical debridement of infected tissue should be urgently performed to limit the further spread of infection. Aggressive surgical debridement of necrotic tissue should take place immediately. This may involve radical facial resections, partial pneumonectomy, colectomy, etc., in accordance with the site of disease. Similar to necrotizing fasciitis, this requires very aggressive surgical management and often carried dramatic morbidity. Unless the immune status can be restored, the outcomes are unfortunately very poor even with the most aggressive therapies and drastic surgical intervention **(23).**

Differential Diagnosis

In a case of mucormycosis in its rhinocerebral form, one must consider different pathologies such as orbital cellulitis and cavernous sinus thrombosis. When we consider the diagnosis of pulmonary mucormycosis, we should think about aspergillosis, nocardiosis, and Wegener's granulomatosis **(32).**

Prognosis

The prognosis is dependent upon the timing of therapeutic intervention, as well as the degree of the underlying immunodeficiency of the patient with mortality ranging from 25% to 87% depending on the site of infection. Severity and poor prognostic indicators include disseminated infection, renal injury, central nervous system disease, and inadequate response to medical treatment. The most important prognostic factor is the ability to restore a normal immune status. If this is not possible, the prognosis is uniformly dismal. If immunocompetence can be restored, even temporarily, then prognosis does improve **(33).**

Complications

Complications of mucormycosis subdivide into those that result from the disease itself and those that are caused by the antifungal treatment. Complications associated with the disease are cavernous sinus thrombosis, disseminated infection, periorbital destruction, palatine ulcers, osteomyelitis, and death. Complications due

to treatment are nephrotoxicity, hypokalemia, prolonged hospitalization (specifically with the use of deoxycholate amphotericin B) **(34).**

Mucormycosis in the COVID-19 Environment:

Even after more than 2 years of its discovery, the coronavirus disease 2019 (COVID-19) is storming the world with rapid infections and has been declared a pandemic by the World Health Organization (WHO). This pandemic has resulted in 531,550,610 infections resulting in 6,302,982 deaths as of June 9, 2020. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection results in upper respiratory illnesses, collectively referred to as COVID-19. Ranging from asymptomatic to flu-like mild symptoms to acute respiratory distress syndrome (ARDS) (G.S.C of the I.C , 2020) , COVID-19 has a variety of symptoms in patients and most of the patients recover on their own **(35).**

However, in patients with ARDS, it is usually fatal. Host immune response is activated upon infection, and hyperactivation of the immune system is believed to cause damage to the lung tissues. A lung biopsy from a COVID-19 patient showed alveolar damage and increased activation of CD4+ and CD8+ lymphocytes **(36).**

While secondary infections during COVID-19 are commonly reported, a surge in mucormycosis infections in COVID-19 patients was surprising during the second wave across the world, especially in India. Mucormycosis cases were reported in the highest number among COVID-19 patients, along with other fungal infections like aspergillosis. While mucormycosis is not a new infection, it is resulting in a huge fatality and morbidity in patients with SARS-CoV-2 infection.The complete pathophysiology of the complication is not yet understood. Therefore, a detailed investigation into the possible causes and treatment options in COVID-19-associated mucormycosis (CAM) is needed. Apart from these, certain cancers, organ transplants, certain supplements, and environmental factors such as personal hygiene have been speculated as potential contributors to CAM. However, a precise understanding of the contributing factors and mechanisms behind CAM is still lacking **(37).**

The Danger of COVID-19-Associated Mucormycosis

Mucormycosis and other fungal infections are caused by fungal species, which are normally present in the environment. Despite being rare compared to bacterial infections, the mortality associated with fungal infections is very high. Certain diseases or medical conditions, which predispose individuals to an immunocompromised state, make patients susceptible to mucormycosis. Various species that cause mucormycosis (Rhizopus oryzae, Mucor circinelloides, Rhizomucor pusillus, Saksenaea vasiformis, Rhizopus microsporus, Apophysomyces variabilis, Lichtheimia ramosa, Cunninghamella bertholletiae) belong to the order Mucorales of the kingdom Fungi. Patients with organ transplants, cancers such as leukemia, Human immunodeficiency virus (HIV) infection, health conditions requiring chronic steroid treatments, usage of immunosuppressive drugs, and most notably uncontrolled diabetes with ketoacidosis, fall in the risk group for mucormycosis and other fungal infections. Additionally, Candida sp. and Aspergillus sp. are also known to cause significant infections in immunocompromised individuals **(38).**

Several Rhizopus sp. are known to cause the most frequent infections, although aspergillosis is also a commonly encountered infection in the risk group of COVID-19 patients. Inhalation of fungal spores present in the air is the major route of infection, although infection through ingestion and skin contact can also occur. ROCM is the most prevalent form of mucormycosis with a very high mortality even with the proper medications. Various mechanisms that contribute to the increased fungal infections include factors such as extensive angioinvasion, increased fungal virulence, and a delay in the diagnosis of the fungal infections **(39).**

Neutrophils are the blood cells implicated in the host defense against fungal infections. Neutrophils migrate toward fungal pathogens and mediate fungal killing through phagocytosis, oxidative stress, and neutrophil extracellular traps (NETs). Neutrophil functions such as migration, oxidative burst, and NET formation are modified in diabetic subjects, leading to decreased clearance of fungal pathogens. Certain fungi such as Rhizopus can metabolize ketone bodies present in the patients with DKA resulting in angioinvasion, thrombosis, and ischemic tissue necrosis. Patients with pulmonary mucormycosis develop symptoms similar to pneumonia, which can also spread to the heart. Mucorale infections have immensely contributed to COVID-19-related ROCM, leading to high rates of mortality and morbidity **(40).**

Renal function in patients with mucormycosis

Rarely, kidney may be involved by contiguous spread from overlying infected incision or from infected donor in renal transplant recipients. As the mucorales infections have an almost universal feature of extensive angioinvasion associated with thrombosis and ischemic necrosis, kidneys are similarly involved in the process with consequent complications. Some data have also demonstrated the ability of R. oryzae sporangiospores or hyphae to adhere to subendothelial matrix proteins and human endothelial cells.

The clinical manifestations of renal mucormycosis depend upon whether the disease is unilateral or bilateral and whether it is disseminated or isolated to the kidney **(41).**

Clinical manifestations of mucormycosis in patients with renal impairment

The common clinical features in this condition described by researchers, were fever (88%), flank pain and tenderness (70%), hematuria and pyuria (70%), and concomitant bacterial urinary tract infection (53%). Acute renal failure was observed in 92% of patients with bilateral renal involvement. As emphasized by these authors, mucormycosis is being increasingly encountered as a cause of otherwise unexplained acute renal failure **(42).**

There have been many similar cases reported in literature. Renal failure is usually the result of near total occlusion of the renal arteries and/or their branches. Both small and large arteries exhibit hyphal invasion and consequent thrombosis leading to massive cortical and medullary infarction. These findings have been confirmed in the kidney biopsy of these patients and at autopsy **(35).**

Besides the extensive ischemic destruction of parenchyma, the histological findings may include the invasion of the glomeruli and tubules by the mucor hyphae. There may be associated giant cell reaction with formation of granulomas in some cases. The mucorales are recognized in Groccot's silver methanamine stained slides by their characteristic morphology. These fungi have broad aseptate hyphae which branch irregularly at right angles as against the septate dichotomously branching hyphae of Aspergillus. Differential diagnosis of acute kidney injury in these patients may be severe pyelonephritis, acute interstitial nephritis and rapidly progressive glomerulonephritis. One can make the correct diagnosis of this condition only if it is suspected early and investigated with laboratory and imaging tests. Since histology is the 'gold standard' of diagnosis, an attempt should be made to get the biopsy of the infected tissue without delay **(43).**

Culture of various body fluids and infected tissues may be sent although it is very uncommon to grow mucorales in culture. Imaging can be a useful diagnostic modality to enable early diagnosis of renal mucormycosis. Besides the ultrasonography suggesting enlarged kidneys, contrast enhanced computerized tomography may reveal the typical features reported earlier. Very recently molecular diagnosis with real time polymerase chain reaction (PCR) has been suggested for an early diagnosis of this condition **(43).**

Treatment

Prognosis of renal mucormycosis is dismal with nearly 100% mortality in patients with bilateral renal involvement and acute kidney injury. Majority of survivors of renal mucormycosis have been those with unilateral renal involvement who received timely appropriate antifungal therapy with nephrectomy. Few exceptions have also been reported in patients with bilateral renal mucormycosis with successful outcome following bilateral nephrectomy and antifungal therapy or medical therapy alone. The four cornerstones of successful therapy are 1) rapid initiation of therapy, 2) reversal of the patient's underlying predisposing condition, 3) administration of appropriate antifungal agents, and 4) surgical debridement of infected tissues i.e. nephrectomy **(44).**

Only 2 systemic antifungal drugs are currently available with good activity against mucorales; Amphotericin B (including the lipid formulations) and the triazole, Posaconazole. Amphotericin-B continues to be the gold standard of antifungal therapy but the conventional formulation is associated with a high incidence of adverse events and resistance in some cases. Patients with renal mucormycosis may benefit from its lipid formulations in view of renal failure that these patients usually have. In addition, we can give higher dose of Amphotericin with lipid formulation for a faster control of disease. Posaconazole, a new triazole, with its pharmacokinetic advantages and low side effect profile, has been increasingly used in mucormycosis both as a "step-down"

therapy following initial amphotericin administration and as a "salvage" therapy in patients with resistance to Amphotericin B **(45).**

References

1. Prakash, H., & Chakrabarti, A. (2021). Epidemiology of mucormycosis in India. Microorganisms, 9(3), 523.
2. Skiada, A., Lass-Floerl, C., Klimko, N., Ibrahim, A., Roilides, E., & Petrikkos, G. (2018). Challenges in the diagnosis and treatment of mucormycosis. Medical mycology, 56(suppl_1), S93-S101.
3. Cornely, O. A., Alastruey-Izquierdo, A., Arenz, D., Chen, S. C., Dannaoui, E., Hochhegger, B., Hoenigl, M., Jensen, H. E., Lagrou, K., & Lewis, R. E. (2019). Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. The Lancet infectious diseases, 19(12), e405-e421.
4. Steinbrink, J. M., & Miceli, M. H. (2021). Mucormycosis. Infectious Disease Clinics, 35(2), 435-452.
5. Serris, A., Danion, F., & Lanternier, F. (2019). Disease entities in mucormycosis. Journal of Fungi, 5(1), 23.
6. Millon, L., Scherer, E., Rocchi, S., & Bellanger, A.-P. (2019). Molecular strategies to diagnose mucormycosis. Journal of Fungi, 5(1), 24.
7. Pilmis, B., Alanio, A., Lortholary, O., & Lanternier, F. (2018). Recent advances in the understanding and management of mucormycosis. F1000Research, 7.
8. Saldanha, M., Reddy, R., & Vincent, M. J. (2021a). of the article: paranasal mucormycosis in COVID-19 patient. Indian Journal of Otolaryngology and Head & Neck Surgery, 1-4.
9. Francis, J. R., Villanueva, P., Bryant, P., & Blyth, C. C. (2018). Mucormycosis in children: review and recommendations for management. Journal of the Pediatric Infectious Diseases Society, 7(2), 159-164.
10. Stone, N., Gupta, N., & Schwartz, I. (2021). Mucormycosis: time to address this deadly fungal infection. The Lancet Microbe, 2(8), e343-e344.
11. Brunet, K., & Rammaert, B. (2020). Mucormycosis treatment: Recommendations, latest advances, and perspectives. Journal de mycologie medicale, 30(3), 101007.
12. Raut, A., & Huy, N. T. (2021). Rising incidence of mucormycosis in patients with COVID-19: another challenge for India amidst the second wave? The lancet Respiratory medicine, 9(8), e77.
13. Chikley, A., Ben-Ami, R., & Kontoyiannis, D. P. (2019). Mucormycosis of the central nervous system. Journal of Fungi, 5(3), 59.
14. Maini, A., Tomar, G., Khanna, D., Kini, Y., Mehta, H., & Bhagyasree, V. (2021). Sino-orbital mucormycosis in a COVID-19 patient: A case report. International Journal of Surgery Case Reports, 82, 105957.
15. Ravani, S. A., Agrawal, G. A., Leuva, P. A., Modi, P. H., & Amin, K. D. (2021). Rise of the phoenix: Mucormycosis in COVID-19 times. Indian journal of ophthalmology, 69(6), 1563.
16. Suganya, R., Malathi, N., Karthikeyan, V., & Janagaraj, V. D. (2019). Mucormycosis: a brief review. J Pure Appl Microbiol, 13(1), 161-165.
17. Sharma, S., Grover, M., Bhargava, S., Samdani, S., & Kataria, T. (2021). Post coronavirus disease mucormycosis: a deadly addition to the pandemic spectrum. The Journal of Laryngology & Otology, 135(5), 442-447.
18. Pakdel, F., Ahmadikia, K., Salehi, M., Tabari, A., Jafari, R., Mehrparvar, G., Rezaie, Y., Rajaeih, S., Alijani, N., & Barac, A. (2021). Mucormycosis in patients with COVID-19: a cross-sectional descriptive multicentre study from Iran. Mycoses, 64(10), 1238-1252.
19. Song, Y., Qiao, J., Giovanni, G., Liu, G., Yang, H., Wu, J., & Chen, J. (2017). Mucormycosis in renal transplant recipients: review of 174 reported cases. BMC infectious diseases, 17(1), 1-6.
20. Hammer, M. M., Madan, R., & Hatabu, H. (2018). Pulmonary mucormycosis: radiologic features at presentation and over time. American Journal of Roentgenology, 210(4), 742-747.
21. Dadwal, S. S., & Kontoyiannis, D. P. (2018). Recent advances in the molecular diagnosis of mucormycosis. Expert review of molecular diagnostics, 18(10), 845-854.
22. Challa, S. (2019). Mucormycosis: Pathogenesis and pathology. Current Fungal Infection Reports, 13, 11-20.
23. Chakrabarti, A. (2021). The recent mucormycosis storm over Indian sky. Indian Journal of Medical Microbiology, 39(3), 269.
24. Smith, C., & Lee, S. C. (2022). Current treatments against mucormycosis and future directions. PLoS pathogens, 18(10), e1010858.
25. Balai, E., Mummadi, S., Jolly, K., Darr, A., & Aldeerawi, H. (2020). Rhinocerebral mucormycosis: a ten-year single centre case series. Cureus, 12(11).
26. Chandra, S., & Rawal, R. (2021). The surge in Covid related mucormycosis. Journal of Infection, 83(3), 381-412.
27. Guinea, J., Escribano, P., Vena, A., Muñoz, P., Martínez-Jiménez, M. d. C., Padilla, B., & Bouza, E. (2017). Increasing incidence of mucormycosis in a large Spanish hospital from 2007 to 2015: Epidemiology and microbiological characterization

of the isolates. PLoS One, 12(6), e0179136.

28. Feng, J., & Sun, X. (2018). Characteristics of pulmonary mucormycosis and predictive risk factors for the outcome. Infection, 46, 503-512.

29. Grimaldi, D., Pradier, O., Hotchkiss, R. S., & Vincent, J.-L. (2017). Nivolumab plus interferon-γ in the treatment of intractable mucormycosis. The Lancet infectious diseases, 17(1), 18.

30. Stemler, J., Hamed, K., Salmanton-García, J., Rezaei-Matehkolaei, A., Graefe, S. K., Sal, E., Zarrouk, M., Seidel, D., Abdelaziz Khedr, R., & Ben-Ami, R. (2020). Mucormycosis in the Middle East and North Africa: Analysis of the FungiScope® registry and cases from the literature. Mycoses, 63(10), 1060-1068.

31. Singh, Y., Ganesh, V., Kumar, S., Patel, N., Aggarwala, R., Soni, K. D., & Trikha, A. (2021). Coronavirus disease-associated mucormycosis from a tertiary care hospital in India: a case series. Cureus, 13(7).

32. Mekki, S. O., Hassan, A. A., Falemban, A., Alkotani, N., Alsharif, S. M., Haron, A., Felemban, B., Iqbal, M. S., & Tabassum, A. (2020). Pulmonary mucormycosis: A case report of a rare infection with potential diagnostic problems. Case Reports in Pathology, 2020.

33. Mehrabi, Z., Salimi, M., Niknam, K., Mohammadi, F., Mamaghani, H. J., Sasani, M. R., Ashraf, M. J., Salimi, A., Zahedroozegar, M. H., & Erfani, Z. (2021). Sinoorbital mucormycosis associated with corticosteroid therapy in COVID-19 infection. Case Reports in Ophthalmological Medicine, 2021.

34. Sreshta, K., Dave, T. V., Varma, D. R., Nair, A. G., Bothra, N., Naik, M. N., & Sistla, S. K. (2021). Magnetic resonance imaging in rhino-orbital-cerebral mucormycosis. Indian journal of ophthalmology, 69(7), 1915.

35. Gebremariam, T., Alkhazraji, S., Alqarihi, A., Wiederhold, N. P., Shaw, K. J., Patterson, T. F., Filler, S. G., & Ibrahim, A. S. (2020). Fosmanogepix (APX001) is effective in the treatment of pulmonary murine mucormycosis due to Rhizopus arrhizus. Antimicrobial Agents and Chemotherapy, 64(6), e00178-00120.

36. Sundaram, N., Bhende, T., Yashwant, R., Jadhav, S., & Jain, A. (2021). Mucormycosis in COVID-19 patients. Indian journal of ophthalmology, 69(12), 3728.

37. Mazzai, L., Anglani, M., Giraudo, C., Martucci, M., Cester, G., & Causin, F. (2022). Imaging features of rhinocerebral mucormycosis: from onset to vascular complications. Acta Radiologica, 63(2), 232-244.

38. Ghosh, D., Dey, S., Chakraborty, H., Mukherjee, S., Halder, A., Sarkar, A., Chakraborty, P., Ghosh, R., & Sarkar, J. (2022). Mucormycosis: A new threat to Coronavirus disease 2019 with special emphasis on India. Clinical Epidemiology and Global Health, 101013.

39. Ghazi, B. K., Rackimuthu, S., Wara, U. U., Mohan, A., Khawaja, U. A., Ahmad, S., Ahmad, S., Hasan, M. M., dos Santos Costa, A. C., & Ahmad, S. (2021). Rampant increase in cases of mucormycosis in India and Pakistan: a serious cause for concern during the ongoing COVID-19 pandemic. The American journal of tropical medicine and hygiene, 105(5), 1144.

40. Mulakavalupil, B., Vaity, C., Joshi, S., Misra, A., & Pandit, R. A. (2021). Absence of Case of Mucormycosis (March 2020–May 2021) under strict protocol driven management care in a COVID-19 specific tertiary care intensive care unit. Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 15(4), 102169.

41. Palanisamy, P. R., & Elango, D. (2022). COVID19 associated mucormycosis: A review. Journal of Family Medicine and Primary Care, 11(2), 418.

42. Vallabhaneni, S., Benedict, K., Derado, G., & Mody, R. K. (2017). Trends in hospitalizations related to invasive aspergillosis and mucormycosis in the United States, 2000–2013. Open forum infectious diseases,

43. Baskar, H. C., Chandran, A., Reddy, C. S., & Singh, S. (2021). Rhino-orbital mucormycosis in a COVID-19 patient. BMJ Case Reports CP, 14(6), e244232.

44. Camps, R. (2018). The treatment of mucormycosis (zygomycosis) in the 21st century. Revista Iberoamericana de Micologia, 35(4), 217-221.

45. Vaughan, C., Bartolo, A., Vallabh, N., & Leong, S. C. (2018). A meta-analysis of survival factors in rhino-orbital-cerebral mucormycosis—has anything changed in the past 20 years? Clinical Otolaryngology, 43(6), 1454-1464.