A REVIEW OF MUCORMYCOSIS: A DEADLY BLACK FUNGUS INFECTION AMONG COVID-19 PATIENTS IN INDIA

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Abstract

In early 2021, the second wave of COVID-19 caused massive chaos in India. As daily infection rates soared, the number of severe cases rose dramatically. The country faced a shortage of healthcare resources, with high demand for hospital beds, medications, vaccines, and oxygen.

Amid this crisis, there was a sudden increase in cases of mucormycosis, a serious fungal infection affecting COVID-19 patients. The most common type seen is the rhino-orbital-cerebral form. Many of these patients had diabetes, a condition that increases the risk of this infection, especially when treated with corticosteroids for COVID-19. This combination can weaken the immune system, making patients more vulnerable to secondary infections.

As new information about this dangerous infection emerges during the pandemic, prevention focuses on managing existing health conditions in high-risk individuals. Recommended treatments include surgery to remove infected tissue and antifungal medications like Amphotericin B and certain azoles. Several guidelines specific to India have been created to help diagnose the infection, understand its symptoms, and monitor its progression. One of the most comprehensive guidelines, called "Code Mucor," suggests a straightforward staging system for the rhino-orbital-cerebral form. A dedicated registry for tracking these cases has also been started.

This review aims to analyze the latest evidence and guidelines regarding COVID-19-associated mucormycosis in India.

1. Introduction

After the COVID-19 pandemic, mucormycosis, also known as "Zygomycosis," became a significant fungal infection that challenged healthcare systems worldwide. It became clear that certain groups, especially people recovering from COVID-19, were at higher risk of developing this serious infection.

Patients with COVID-19 faced various complications, including heart issues and secondary infections, which increased their risk during recovery. Studies showed that immune suppression or pre-existing health conditions played a major role in the development of mucormycosis. The fungus usually enters the body through the respiratory tract, particularly the nose and sinuses, and can spread to the eyes and brain. Early diagnosis and treatment are crucial for better outcomes and to reduce complications.

Advances in diagnostic techniques have made it possible to identify mucormycosis through methods like direct microscopic analysis, histopathology, and PCR-based tests. These improved diagnostic methods have helped enhance patient outcomes. However, the mortality rate associated with mucormycosis remains a concern, affecting various populations.

While the exact cause of mucormycosis in COVID-19 patients isn't fully understood, experts believe that the use of steroids

during treatment may weaken the immune system, making patients more vulnerable to fungal infections. Researchers have noted that coexisting fungal infections with COVID-19 might lead to misdiagnoses, drawing from lessons learned during previous outbreaks of SARS and influenza. Patients with weakened immune systems were particularly at risk for severe fungal infections.

Looking ahead, the experiences from the COVID-19 era highlight the need for careful management of infectious diseases. It is crucial to minimize immunosuppression in COVID-19 treatment to lower the risk of mucormycosis. Ongoing research and awareness will be essential to tackle new infections. In 2023 and beyond, healthcare systems should continue implementing strong safety measures to protect patients, especially those recovering from COVID-19. Improved infection control and early detection methods will help in preventing and managing mucormycosis. Collaboration among experts, scientists, and healthcare professionals will be vital in effectively addressing future health challenges.

2. Origin of mucormycosis

Mucormycosis, also known as zygomycosis or "black fungus," is a serious and rare fungal infection caused by molds called mucormycetes. These fungi belong to the subphylum Mucoromycotina and the order Mucorales. Mucorales fungi are frequently found in patients with blood cancers, those undergoing stem cell transplants, and solid organ transplant recipients, second only to Aspergillus fungi.

There are about 27 species of Mucorales that can cause mucormycosis, with the most common genera being Rhizopus, Mucor, and Lichtheimia. These fungi are usually found in soil, decaying food, manure, and dust. Mucormycosis was first reported in humans in 1855, and later cases included pulmonary mucormycosis in cancer patients in the late 1800s. The main ways to get infected are by inhaling spores, eating contaminated food, or having the fungi enter through cuts or abrasions. Outbreaks have also been linked to contaminated medical devices and hospital supplies.

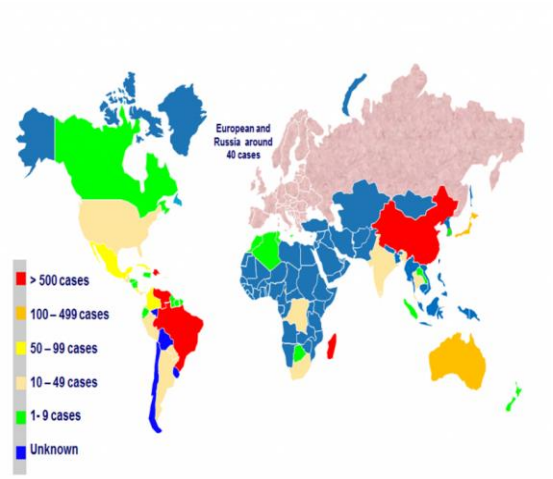
This infection primarily affects people with weakened immune systems, such as those with diabetes, cancer, or those taking immunosuppressive medications. Diagnosis is typically made through laboratory tests on tissue samples from the infected area, and imaging tests like CT scans can also help.

Mucormycosis can occur in several forms, including rhino-orbital cerebral mucormycosis (ROCM), pulmonary, cutaneous (skin), gastrointestinal, disseminated (spread throughout the body), and uncommon sites. ROCM is the most common type, often associated with the Rhizopus species. Other species can cause different forms of the disease, such as Cunninghamella in pulmonary infections and Apophysomyces in cutaneous infections.

The most common sites of infection are the sinuses (39%), lungs (24%), disseminated infections (23%), and skin (19%). The fungi invade blood vessels, causing blood clots and tissue damage. In healthy individuals, the immune system usually eliminates these fungi. However, Mucorales can be resistant to some immune responses, making them more dangerous.

Despite the rise in mucormycosis cases, accurate data on its prevalence is lacking. Studies show that most cases occur in Europe (34%), followed by Asia (31%), the Americas (28%), Africa (3%), and Australia/New Zealand (3%). The Leading International Fungal Education (LIFE) estimates around 10,000 cases globally, not including India, where the numbers jump significantly.

In India, the prevalence is 0.14 cases per 1,000 people, much higher than in developed countries. The mortality rate for mucormycosis is high, at about 54%, and varies based on the infection site and underlying health issues. Disseminated mucormycosis has the highest mortality rate (96%), followed by pulmonary (76%) and sinus (46%) infections.



(Mucormycosis infection rates around the world)

3. Pathogenesis of mucormycosis

The spores of the fungi usually spread through the air and can enter the human body by inhalation, through skin lesions, or via the gastrointestinal tract. Once inside, the fungi go through several important steps to grow and spread. These steps include:

1. Spore Inoculation: The spores attach to and enter the body.
2. Avoiding Immune Response: The fungi must escape detection and destruction by immune cells like macrophages and neutrophils.
3. Germination: The spores begin to grow into hyphae (the branching structures of the fungus).
4. Utilizing Host Conditions: The fungi thrive in certain conditions, such as iron overload or ketoacidosis (a condition often related to diabetes).
5. Attachment to Blood Vessel Lining: They attach to the lining of blood vessels using specific receptors.
6. Damage to Blood Vessels: Through endocytosis, the fungi can harm the endothelial cells (the cells lining the blood vessels), leading to tissue death, blood clot formation, or bleeding.

These processes can contribute to problems in multiple organs.

3.1. iron role in mucormycosis

Mucorales species can thrive in environments with high iron levels, which is especially relevant in conditions like diabetic ketoacidosis, where unbound iron in the blood can lead to mucormycosis. Normally, iron levels in the blood are kept low by binding to proteins such as transferrin, lactoferrin, and ferritin. This is a key defense mechanism of the body against Mucorales infections.

The fungus acquires iron using specialized proteins called iron permeases or siderophores, which help convert ferric iron into a more soluble ferrous form. This ferrous iron is then absorbed by protein complexes known as multicopper oxidase, and the genes responsible for these proteins

have been linked to the virulence of fungal infections in animal models of mucormycosis.

Additionally, Mucorales can extract iron from the host by using heme. For example, Rhizopus oryzae can obtain iron from hemoglobin in the host's blood, which contributes to its aggressive, angioinvasive behavior. The breakdown of heme through enzymes called heme oxygenases releases ferric iron inside the fungus, supporting its growth.

3.2. Possible pathways for the fungal spores to enter in COVID patients

Mucormycosis is commonly seen in individuals with diabetic ketoacidosis and those with weakened immune systems, resulting in a 100% fatality rate in severe cases. The location of the infection, such as rhino-cerebral mucormycosis, greatly affects its severity. In particular, Rhino-Orbito-Cerebral Mucormycosis is especially dangerous because it can cause vision loss and seizures, potentially leading to death.

The fungal spores can enter the body through various routes, including ingestion, contact with wounds, and inhalation. Additionally, contamination from medical supplies like bandages, ostomy bags, and linens can contribute to invasive fungal infections in COVID patients in hospitals. Previous reports have indicated outbreaks of healthcare-associated mucormycosis, with infections entering through surgical instruments and medical devices such as catheters, adhesive tape, bandages, wooden tongue depressors, and damaged water systems, as well as construction in nearby buildings. These outbreaks are particularly severe in neonatal, hematological, and transplant units.

There is also a risk of inhaling spores during hospitalization. The immunosuppressive effects of medications used to treat COVID can make individuals more vulnerable to infection, either during their hospital stay or after discharge. Patients often have higher levels of iron in their blood, which creates a favorable environment for fungal growth, leading to further infections and mucormycosis. The survival of these spores depends on suitable conditions, and the presence of iron can help them remain viable for longer periods.

3.3. immunosuppression in covid-19 and mechanism of action of dexamethasone

The main anti-inflammatory effect of dexamethasone works by blocking pro-inflammatory genes that trigger acute inflammation, which can lead to a cytokine storm. In coronavirus infections, dexamethasone is used to lower inflammation by down-regulating specific genes, including Aryl hydrocarbon receptors and Indoleamine 2, 3-Dioxygenase 1.

How dexamethasone works depends on the dosage. Low doses act slowly through genomic mechanisms, taking longer to show effects and causing fewer side effects. On the other hand, higher doses work more quickly through non-genomic pathways but come with more severe side effects. Clinical research has shown that corticosteroids, particularly dexamethasone, are effective against COVID-19 and pneumonia in both laboratory and real-life situations. Lower doses of dexamethasone have been found to reduce mortality, especially in patients with

severe COVID symptoms. However, it is important to use it carefully, as higher doses can be harmful.

After randomized controlled trials, the U.K. announced that dexamethasone was the first drug shown to reduce mortality by one-third among critically ill patients on ventilators. Observational studies confirmed that corticosteroids can lower short-term mortality and reduce the need for mechanical ventilation. However, researchers emphasized the need for more clinical data, as prolonged use of steroids could lead to secondary infections.
Raju et al. reviewed global clinical trial registries and found that out of 60 trials, 11 reported improved respiratory rates in patients treated with corticosteroids for COVID-19. Another study involving 2,104 patients showed that dexamethasone reduced 28-day mortality among those needing invasive mechanical ventilation or oxygen, but not among those who did not need respiratory support. This indicates that glucocorticoids help limit lung injury from inflammation and reduce the risk of respiratory failure and death.

However, some evidence suggests that corticosteroids may increase viral load in patients after infection. This means that while dexamethasone can be effective for short-term treatment, long-term use might weaken the body's defense systems.

A survey of 73 studies involving 21,350 COVID-19 patients treated with corticosteroids showed that the drug helped severely ill patients recover, but it had no significant effect in either high or low-dose regimens. Interestingly, recent reports indicated that low-dose corticosteroids did not significantly affect the duration of SARS-CoV-2 viral shedding.

In conclusion, while many treatment options, including corticosteroid therapy, have been explored, the effectiveness of these treatments against the infection remains uncertain. The success of dexamethasone depends on the dosage and severity of the illness, and potential side effects can push patients into an immunosuppressed state. COVID-19 is a multi-organ disease, so it is important to not only focus on the virus but also to provide comprehensive care for the whole body. This reflects Sir William Osler's saying: The good physician treats the disease; the great physician treats the patient who has the disease.

4. Clinical manifestations

Mucormycosis is a fungal infection that includes several types, such as chromoblastomycosis, mycetomas, sinusitis, and superficial, subcutaneous, cutaneous, and systemic phaeohyphomycosis. It is classified into five main patterns: (1) rhinocerebral (2) cutaneous (3) pulmonary (4) gastrointestinal and (5) disseminated. There are also rare forms like peritonitis, endocarditis, osteomyelitis, and renal infections. The most common sites of infection are the sinuses, lungs, and skin, with dissemination occurring in 23% of cases. The mortality rates are high: 96% for disseminated mucormycosis, 85% for gastrointestinal infections, and 76% for pulmonary infections. Infants are more vulnerable than adults.

Diabetes mellitus is linked to rhinocerebral mucormycosis, while hematological malignancies are associated with

disseminated forms. Trauma often leads to cutaneous mucormycosis, and solid organ transplantation can result in pulmonary, gastrointestinal, or disseminated infections. In India, rhinocerebral mucormycosis is the most common type, followed by cutaneous and pulmonary infections.

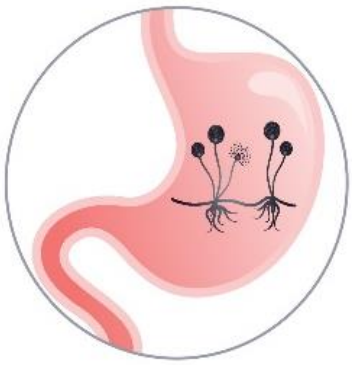
(a) Rhinocerebral Mucormycosis: This is the most prevalent form. It starts when spores are inhaled into the nasal passages and can spread to the brain through the orbital area. Symptoms include fever, headaches, facial numbness, and pain, along with nasal discharge, sinusitis, and black necrotic tissue. Ocular symptoms can include eye pain, visual changes, and swelling. Imaging often shows thickened nasal linings, sinus issues, and potential damage to nearby bones. Once the infection reaches the brain, the mortality rate rises sharply.

(b) Pulmonary Mucormycosis: This type can be mistaken for pulmonary Aspergillosis. Symptoms include a high fever and a nonspecific cough, and in diabetic patients, it can cause airway obstruction. Chest imaging may show lung consolidation and various nodules. A classic sign is the reversed halo sign, usually seen in the upper lobe of the lung.

(c) Cutaneous Mucormycosis: This type can occur through direct skin contact or through the spread from other infected areas. It typically presents as fast-growing ulcers with a red halo. Secondary infections can cause necrotic lesions and are often associated with rhinocerebral infections.

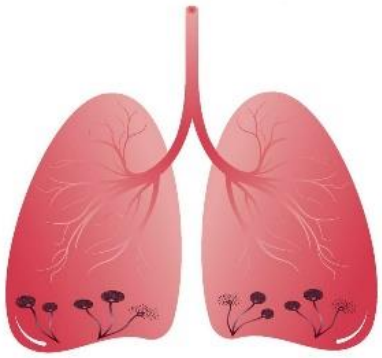
(d) Gastrointestinal Mucormycosis: This is rare and primarily affects the large intestine, stomach, and small intestine. Symptoms are often nonspecific and can include abdominal pain and bleeding. This type is more common in premature infants and malnourished patients, with a high mortality rate.

(e) Disseminated Mucormycosis: This severe form involves multiple organ systems and typically occurs in critically ill patients. It often starts from the lungs, gastrointestinal tract, or skin.



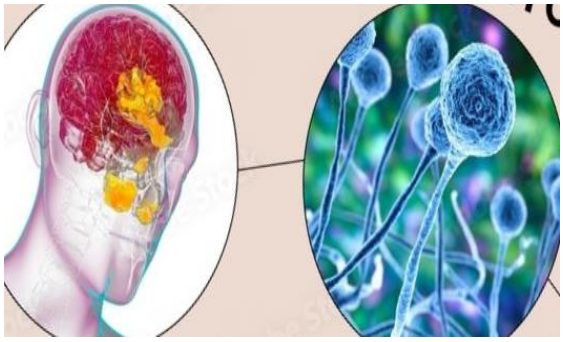
Phylogenetic Analysis: The study explores the genetic relationships among Mucorales fungi based on their internal transcribed spacer regions. Different species are associated with various clinical manifestations. For instance, Apophysomyces, Lichtheimia, and Saksenaea are more commonly found in cutaneous cases, while Rhizopus is linked to rhinocerebral infections. The analysis shows distinct clusters of these fungi, suggesting that the type of infection is influenced by the species present. Overall, the species dominance helps determine the clinical form of mucormycosis.

Gastrointestinal Mucormycosis



Cutaneous mucormycosis

Pulmonary Mucormycosis



Rhino Cerebral Mucormycosis

5. Antifungal Properties of Nanoparticles Against Black Fungus Associated with COVID-19

The COVID-19 pandemic has led to an increase in cases of black fungus, or mucormycosis, particularly in patients with weakened immune systems. This fungal infection can be severe and hard to treat. Researchers are exploring nanoparticles as a potential solution to combat this infection effectively.

What are Nanoparticles:

Nanoparticles are tiny particles that are usually less than 100 nanometers in size. Because of their small size, they have unique properties that make them useful in medicine, especially in treating infections.

Types of Nanoparticles Used Against Black Fungus

(a) Silver Nanoparticles:

. Effectiveness: known for their strong antifungal properties, AgNPs can kill fungi by disrupting their cell walls and generating harmful reactive oxygen species.

. Application: They are being explored as coatings for medical devices or as additives in antifungal treatments.

(b) Gold Nanoparticles:

. Effectiveness: These nanoparticles can inhibit fungal growth and are often used in drug delivery systems.

. Application: Gold nanoparticles can be combined with antifungal drugs to enhance their effectiveness.

Zinc Oxide Nanoparticles:

. Effectiveness: ZnO NPs have antifungal properties and can damage fungal cell membranes.

. Application: They are being researched for use in creams and ointments to treat fungal infections.

(c) Chitosan Nanoparticles:

. Effectiveness: Made from chitin (found in shellfish), these nanoparticles have antimicrobial properties and can enhance the delivery of antifungal agents.

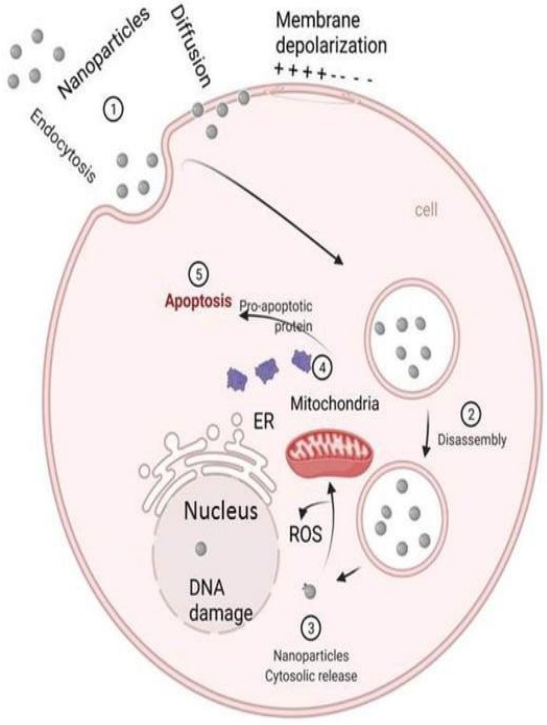
. Application: Chitosan nanoparticles can be used to create biodegradable packaging or coatings that prevent fungal growth.

(d) Magnetic Nanoparticles:

. Effectiveness: These can be used to target and deliver antifungal drugs directly to infected areas, improving treatment precision.

. Application: They allow for the controlled release of drugs in the body.

Nanoparticles, such as silver, gold, zinc oxide, chitosan, and magnetic nanoparticles, show great promise in treating COVID-19-linked black fungus. They can effectively inhibit fungal growth, combat drug resistance, and enhance the delivery of antifungal medications, potentially leading to better treatment outcomes for patients.



(Mechanism of Antimicrobial Action of Nanoparticles Against Fungi Nanoparticles inhibit fungal growth by penetrating cells via endocytosis and diffusion, ultimately leading to apoptosis. Once inside the cells, nanoparticles disrupt the synthesis of the cell wall and membrane, interfere with energy transduction, generate reactive oxygen species, inhibit enzymes, and reduce DNA synthesis, causing DNA and protein damage).

6. Signs and Symptoms of Mucormycosis

During treatment or after recovering from COVID-19, patients may experience fever, headaches, and reddish swelling on the nose and around the eyes. These are significant signs of mucormycosis.

Patients have also reported issues such as changes in vision, swelling around the eyes, eye pain, facial swelling, and difficulty breathing. Diabetic patients may experience double vision, which can indicate an infection.

In medical terms, key symptoms of mucormycosis include sinus pain, bulging of the eyes (proptosis), swelling around the eyes, problems at the back of the eye (orbital apex syndrome), sores in the mouth (palate ulcers), and weakness or loss of function in facial nerves (cranial nerve palsy).

7. Diagnosis of Mucormycosis

Diagnosing mucormycosis can be challenging, but with the right approach, doctors can identify it based on specific symptoms, detailed patient history, careful clinical evaluation, and specialized tests.

(a). Symptoms and History: Doctors look for characteristic symptoms and take a thorough history of the patient's health.

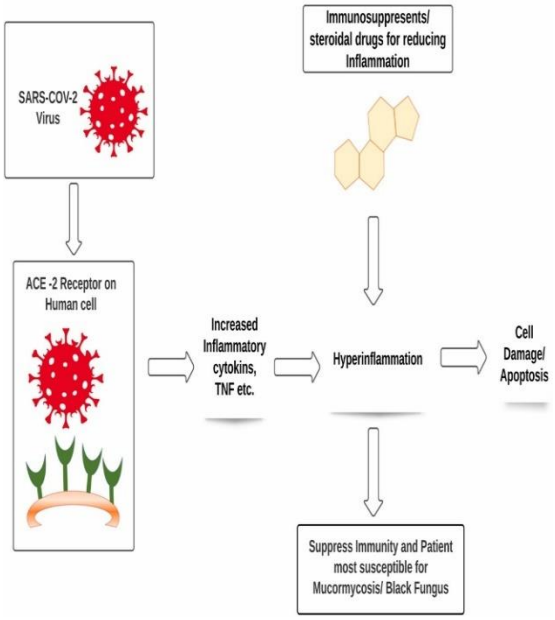
(b). Histopathology: Examining infected tissue under a microscope helps distinguish mucormycosis from other fungal infections like aspergillosis. Mucorales fungi produce wide, thin-walled, ribbon-like structures that are typically non-pigmented.

(c). Direct Microscopy: Using a method called wet mounts with special fluorescent dyes can help visualize the characteristic fungal structures quickly.

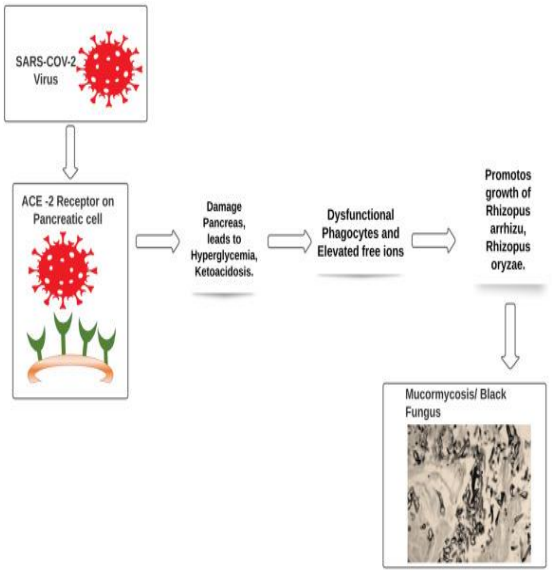
(d). Culture Tests: Growing samples in the lab is important because mucorales fungi can grow quickly at temperatures between 24 and 37 °C, usually within 24 to 48 hours. This method helps identify the specific type of fungus.

(e). Blood Tests: Researchers have found that detecting circulating DNA in the blood using a technique called quantitative polymerase chain reaction (qPCR) can help diagnose mucormycosis, especially in cases where traditional methods are difficult. This method is specific and does not confuse mucormycosis with other common fungal infections like Fusarium or Aspergillus. It is also useful for patients who cannot have a biopsy, such as those with certain blood disorders.

Early diagnosis is crucial for effective treatment, so if you have symptoms of mucormycosis, it's important to seek medical help promptly.



(In severe cases of COVID-19, patients may experience immune system dysfunction, leading to a decrease in lymphocyte counts and a significant increase in inflammation).



(SARS-CoV-2 enters cells through its spike protein, which binds to angiotensin-converting enzyme 2 (ACE2) receptors).

8. Treatment for Mucormycosis (Black Fungus)

Early diagnosis, addressing risk factors, timely antifungal treatment, and surgical removal of all infected tissue are crucial for

effectively treating mucormycosis. Due to limited diagnostic tools, about 50% of cases are only identified post-mortem. Diagnosis is feasible for rhino-cerebral and skin infections using imaging studies and nasal endoscopy. Research has shown that a PCR method can detect mucorales DNA in blood samples three days before a formal diagnosis of mucormycosis. Therefore, if a COVID-19 patient with diabetes reports headaches and visual disturbances, it's essential to evaluate them for mucormycosis through imaging and nasal endoscopy, as early detection can save lives by preventing the fungus from spreading to the brain.

Managing or eliminating predisposing factors is vital for effective treatment. Diabetes, particularly with ketoacidosis, is a significant concern for many patients, so controlling blood sugar and reversing ketoacidosis can help prevent mucorales from invading tissues. Some studies suggest that using sodium bicarbonate with insulin may reverse diabetic ketoacidosis. Additionally, minimizing the use of immunosuppressive drugs, especially steroids and deferoxamine, can help limit the fungus's invasion.

Surgical removal of infected tissue is the most effective treatment for mucormycosis. While this is easier in cases like rhino-cerebral or skin infections, it can be difficult or impossible for pulmonary infections or brain involvement. Studies indicate that early surgical removal of infected sinuses in rhino-cerebral mucormycosis can prevent the infection from spreading to the eyes, resulting in cure rates as high as 85%. Furthermore, combining surgery with antifungal agents can reduce mortality from 70% to 14%.

Amphotericin B is widely regarded as the preferred antifungal drug for treating mucormycosis. Liposomal formulations, which have lower toxicity and better central nervous system penetration, are recommended at doses ranging from 5 mg/g/day to 10 mg/kg/day for cerebral infections. The treatment duration varies based on the patient's condition, with some guidelines suggesting at least three weeks of therapy. If improvement is noted, treatment may continue with triazoles like posaconazole, which has emerged as a strong alternative to amphotericin B. While posaconazole is more effective than itraconazole, it is less effective than amphotericin B. Both intravenous and oral forms enhance the drug's bioavailability.

Although itraconazole shows some activity against mucorales in laboratory settings, it has not proven effective in clinical trials, and voriconazole has failed against mucorales in vitro, indicating that triazoles should not be the first-line treatment. In studies with animal models, caspofungin showed minimal activity against mucorales alone but had a synergistic effect when combined with amphotericin B, demonstrating low toxicity. Additionally, low doses of caspofungin effectively inhibit a specific enzyme produced by Rhizopus oryzae.

Other supportive therapies include iron chelators, excluding deferoxamine, which can hinder fungal growth by limiting its access to iron, as deferoxamine actually promotes mold growth. The use of hyperbaric oxygen therapy can also inhibit

mucormycosis by enhancing neutrophil function against the fungus.

9. Conclusion

A group of diabetic COVID-19 patients who receive treatment with steroids, oxygen, or spend a long time in intensive care can develop a severe fungal infection called rhino-orbito-cerebral mucormycosis. It's essential for radiologists to be alert for early signs of this condition because it can lead to serious complications, including blindness, stroke, and even death within just 48 hours. Early detection allows for immediate antifungal treatment, which can reduce the risks of severe outcomes.

Imaging tests are vital to determine how far the disease has spread and to plan necessary surgical procedures to remove infected tissue. Removing all dead tissue greatly increases the chances of survival. The best imaging methods to use are contrast-enhanced MRI and plain CT scans. A typical sign of localized infection on these images is called the "black turbinate."

In more advanced cases, there may be signs of dead or damaged soft tissue in the eye area and the central skull base. Lesions in the nose and surrounding areas that do not enhance on imaging are due to tissue damage caused by the fungus. The fungus can spread through blood vessels and nerves without affecting the bones right away. Evaluating these non-enhancing lesions is crucial, as they are a key factor in predicting the risk of death from this specific fungal infection.

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