A REVIEW ARTICLE ON MUCORMYCOSIS: A CHALLENGING AND DEADLY DISEASE IN COVID 19

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Abstract:

Patients with respiratory viral infections, like COVID-19, are at a higher risk of developing co-infections, which can lead to increased fatality rates. One significant concern is mucormycosis, a serious fungal infection caused by fungi from the Mucorales group. This condition poses a "double threat" during the COVID-19 pandemic, particularly affecting immunocompromised individuals. Mucormycosis often begins in the sinuses (39% of cases), lungs (24%), or skin (19%), and can spread to other areas in about 23% of cases. Unfortunately, the mortality rate for disseminated mucormycosis is extremely high, reaching 96%. Symptoms are typically nonspecific and can mimic those of other bacterial or fungal infections, making diagnosis challenging. Since the onset of the COVID-19 pandemic, cases of COVID-19-associated mucormycosis (CAM) have been reported in various countries, including the USA, Turkey, France, Mexico, Iran, Austria, the UK, Brazil, and Italy. However, India has emerged as a hotspot, with around 28,252 cases reported by June 8, 2021. CAM typically strikes patients 12 to 18 days after they recover from COVID-19, and around 80% of those affected may require surgery. If diagnosis and treatment are delayed, the mortality rate can soar to 94%. In some cases, COVID-19 is the only identifiable risk factor for developing CAM. This information underscores the need for healthcare professionals and researchers to focus on mucormycosis, aiming to bridge the gap between clinical knowledge and potential treatments for this opportunistic fungal infection.

Evolution: *Mucormycosis is rare but life threatening infection affecting less than 1.7/million population each year. First case of mucormycosis was described by Friedrich Kuchenmeister in 1855 [8]. Furbringer first described the disease in lungs in 1876.In 1884, Lichtheim established the development of the disease in rabbits and described two species which later known as Lichtheimia and Rhizopus.*

Keywords: Mucormycosis, Types, Treatments, Black fungus Mucorales Mucormycosis COVID-19 DKA Angioinvasion Liposomal amphotericin B, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), COVID-19 associated Mucormycosis (CAM), hyperglycemia, Covid 19, Pandemic, Epidemic, Diabetes, Mechanism, Classification, Histology.

Introduction

The novel coronavirus, known as SARS-CoV-2, was first identified in Wuhan, China, on December 21, 2019. Since then, it has spread quickly, impacting millions of people around the world. On March 11, 2020, it was officially declared a pandemic. By June 2021, there were about 172 million confirmed cases and 3.69 million deaths globally. The most common symptoms of COVID-19 include cough, fever, and difficulty breathing.

The COVID-19 pandemic and co-infection with mucormycosis are serious challenges currently faced by humanity. Mucormycosis is a straightforward but dangerous fungal infection that invades blood vessels, has a rapid onset, and leads to high fatality rates. It is recognized as the second most common mold infection

affecting people with weakened immune systems.

Mucormycosis is a rare but serious life threatening angioinvasive, non- contagious with high mortality rate caused by a group of molds called mucormycetes. These fungi live throughout the environment, particularly in soil and in decaying organic matter, such as rotten wood leaves or compost piles.

The phylum Zygomycota includes a group of lower fungi known for their typically non-septate (coenocytic) structures and the formation of zygospores after the fusion of their reproductive cells. Mucormycosis, also called zygomycosis, is caused by molds from the order Mucorales. This order consists of six families that are important for human and animal diseases, with most human cases stemming from the Mucoraceae family, which includes genera like Absidia, Mucor, Rhizomucor, and Rhizopus. Other pathogenic families include Cunninghamellaceae and Saksenaceae, but the most common cause of human infections is Rhizopus oryzae.

People can develop mucormycosis by coming into contact with fungal spores in the environment. For instance, inhaling spores can lead to infections in the lungs or sinuses. These infections are more likely to occur in individuals with health issues or those taking medications that weaken their immune systems. Mucormycosis can also affect the skin if the fungus enters through cuts, scrapes, burns, or other skin injuries.

Classification and Clinical Manifestation:

Type	Pathogenesis	Clinical Manifestation	Risk Factors
Rhino-cerebral mucormycosis	Spores invade sinuses, cribriform plates, and through the cavernous sinus.	Infects the sinuses and spreads to the brain. Destroys maxillary-facial structures and causes ptosis, proptosis, and permanent vision loss [37].	Common in patients with uncontrolled diabetes [49] and kidney transplant.
Pulmonary mucormycosis	Spread of fungal infection through the bloodstream.	Destroys bronchial airways, causes dyspnoea, tracheal invasions of the lungs, and a reverse halo sign on CT scan.	Patients with cancer, post-transplant immunosuppressive therapy [21].
Gastrointestinal mucormycosis	Inhaling spores that invade the GI tract.	Fever, bowel, and per rectal bleed [45,50].	Consistent use of broad-spectrum antibiotics, malnutrition, and neutropenia.
Cutaneous mucormycosis	Direct inoculation of skin through site of trauma or thermal burns.	Black discolouration and lesions on the skin.	Skin trauma such as surgery or burns. It does not involve an impaired immunological response.
Disseminated mucormycosis	Occurs when the infection spreads through the bloodstream to another part of the body	Commonly affects the brain, but also other organs such as the spleen, heart, and skin.	Iron overload, neutropenia, suppressed immune system [24].

Rino-Cerebral Mucormycosis: Rhino-orbital-cerebral mucormycosis is the most common form of this fungal infection. It typically begins when spores are inhaled into the nasal passages, allowing the infection to spread from the sinuses to the brain through the eye area.

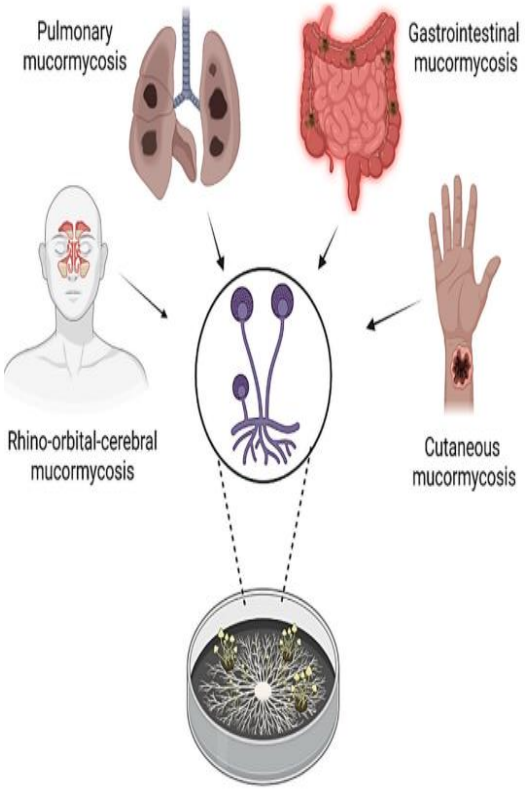
Initial symptoms can include fever, headaches, facial numbness, and pain, often accompanied by nerve issues, nasal discharge, ulcers in the nose, sinusitis, paralysis on one side of the body, black necrotic tissue (eschars), and mental decline. These early signs can resemble those of bacterial sinusitis. optic neuritis, bone weakening, tissue death, brain abscesses, and erosion of skull bones.

Ocular symptoms may include eye pain, changes in vision, bulging eyes (proptosis), swelling (chemosis), drooping eyelids (ptosis), paralysis of eye muscles (ophthalmoplegia), infection around the eye (orbital cellulitis), and discoloration of the skin around the eyes, along with necrosis.

Imaging tests typically show a thickened mucosal lining, sinusitis with varying degrees of damage, and erosion of bones in

the nasal septum, orbit, and jaw. As the infection progresses, it can lead to more severe issues like soft tissue infiltration, orbital cellulitis, inflammation of the optic nerve

The infection primarily follows pathways through the nasal and orbital areas, specifically the ethmoid and sphenoid sinuses and the superior orbital fissure. It can reach the brain through nerve pathways or the cribriform plate. The pterygopalatine fossa has been identified as a reservoir for the fungi. The risk of death significantly increases once the infection invades the cranial area. Cerebral infections can also spread from other parts of the body through the bloodstream.



Pulmonary Mucormycosis: Pulmonary mucormycosis often presents in ways that can be confused with pulmonary aspergillosis. Patients typically experience a high fever (over 38°C) that doesn't improve with broad-spectrum antibiotics. Common symptoms include a nonspecific cough, and in some cases, difficulty breathing (dyspnea), coughing up blood (hemoptysis), and chest pain that feels worse with breathing (pleuritic chest pain). Diabetic patients are particularly at risk and may develop lesions in the airways, leading to airway obstruction and lung collapse. Imaging studies for pulmonary mucormycosis usually

show lung infiltration, consolidation, thick-walled cavities, multiple nodules, pleural effusion, and swollen lymph nodes in the chest (hilar/mediastinal lymphadenopathy). One hallmark of pulmonary mucormycosis is the "reversed halo sign," which is typically seen on imaging. This sign usually appears in one lung (most often in the upper lobe, followed by the lower lobe and middle lobe) and is rarely bilateral.

Cutaneous Mucormycosis:

Cutaneous mucormycosis is divided into two types: primary and secondary.

Primary cutaneous mucormycosis occurs when the fungus directly enters the skin, often due to a break in the skin barrier. This type can be further categorized into two forms:

1. Localized infection, which affects either the superficial or deep layers of the skin in 32–56% of cases.
2. Deep infection, which extends into bones or muscles in 24–52% of cases. Additionally, about 16–20% of cases show spread of the infection through the bloodstream, leading to secondary mucormycosis.

Secondary cutaneous mucormycosis typically arises from the spread of infection from other areas of the body, often from a rhinocerebral infection. Clinically, cutaneous mucormycosis appears as dry,

rapidly growing ulcers with a red halo. In secondary cases, it may present with necrotic lesions, characterized by red edges and black tissue (eschar), along with necrosis in the orbital, nasal, or palatal areas due to the spread from the initial rhinocerebral infection.

Gastrointestinal Mucormycosis: Gastrointestinal infections primarily affect the large intestine (about 43.2%), followed by the stomach (33%) and small intestine (28.4%). In adults, infections are more common in the stomach, while children are more likely to have issues in the intestines. The symptoms of these infections are often nonspecific, making diagnosis challenging. Common symptoms include fever, abdominal pain, gastrointestinal bleeding, and changes in bowel habits. These infections are particularly serious in premature newborns and malnourished patients, with a high mortality rate of 85% in these groups.

Desiminated Mucormycosis: All of the infections mentioned can potentially develop into disseminated mucormycosis, a severe form that affects multiple distant organ systems. This is very rare and typically occurs in people with severely weakened immune systems or those receiving deferoxamine treatment. Dissemination often starts in the lungs, gastrointestinal tract, or through trauma and deep skin injuries. The brain is frequently targeted after the infection spreads through blood vessels, and it can also spread to the heart, liver, spleen, and other organs

Pathophysiology of Mucormycosis:

Mucormycosis, previously known as zygomycosis, is a serious fungal infection caused by fungi from the Mucorales group, with *Rhizopus* and *Mucor* being the most common culprits. These fungi thrive in warm, humid environments and can infect people when their spores are inhaled or enter through skin wounds.

The risk of developing mucormycosis is particularly high in immunocompromised individuals, such as those with diabetes, chronic kidney disease, malignancies, or those taking immunosuppressive drugs. Diabetes, especially when complicated by ketoacidosis, is a major risk factor because the acidic environment can impair immune cell function, making it easier for the fungi to invade.

In a healthy immune response, macrophages and neutrophils help fight off these fungal spores. However, when the immune system is weak, the spores can germinate into hyphae and cause infection. In diabetic patients, high levels of unbound iron in the blood can fuel the growth of *Rhizopus, which thrives in acidic conditions. Additionally, during high blood sugar levels, a receptor called GRP78 on *Rhizopus* can bind more effectively to cells in vital organs, increasing tissue damage.

Mucormycosis has been increasingly reported in patients with COVID-19, particularly those treated with corticosteroids, which can suppress immune function. The SARS-CoV-2 virus also alters the immune response, further elevating the risk of fungal infections.

In summary, mucormycosis is a dangerous fungal infection that primarily affects individuals with weakened immune systems, particularly those with diabetes or undergoing certain treatments, like those for COVID-19.

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Symptoms of Mucormycosis:

1]Rino-orbital Cerebral Mucormycosis:
1. Vision loss
2. one sided headache behind the eyes facial
pain
3.nasal discharge
4.sinusitis
5.black patches on nose and inner
2]Pulmonary Mucormycosis:
1.fever
2.cough
3.chest pain
4.shortness of breath
3]Cutaneous Mucormycosis:
1.skin discolouration
2.pain
3.swelling
4]Gastrointestinal Mucormycosis:
1.abdominal pain
2.vomiting
3.gastrointestinal bleeding
4.gastric ulcers
5]Disseminated Mucormycosis:
1.thrombotic endocarditis
2.brain infection

Hisopathology of Mucormycosis:

Mucormycosis is typically diagnosed through direct microscopic examination of samples. To enhance the visibility of the fungal hyphae, special fluorescent dyes like blankophor and calcofluor white are used in combination with potassium hydroxide (KOH). The infection is confirmed by observing characteristic hyphal features using various staining methods, such as hematoxylin and eosin stain, periodic acid-

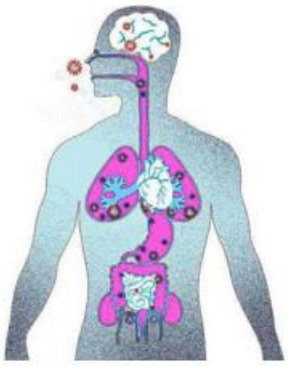
Schiff stain, or Grocott-Gomori's methenamine silver stain.

When examining tissue samples, it's important to note that tissue processing can lead to the formation of pseudo-septae or distort the typical 45° branching angle of the hyphae. Therefore, the wide, irregular ribbon-like structure of the hyphae is a more reliable indicator for diagnosis. In acute infections, you may see signs of tissue damage like hemorrhagic infarcts, coagulative necrosis, invasion of blood vessels, and inflammation from neutrophils (especially in patients with a normal immune response). In chronic cases, a type of inflammation known as pyogranulomatous inflammation may occur, often with hyphae surrounded by a distinctive immune response called the Splendore-Hoeppli phenomenon.

Despite these characteristics, lesions can be nonspecific and mucormycosis is sometimes mistakenly diagnosed as aspergillosis. To improve diagnosis, immunohistochemistry techniques using monoclonal antibodies can differentiate between these two fungal infections. For initial identification, growing the fungi on solid media can help determine their genus and species, and also assess antifungal susceptibility.

Transmission:

Spores from the environment can spread in several ways: through breathing them in, through cuts or wounds, or by eating contaminated food. While these occurrences are rare, several factors in healthcare settings have been linked to outbreaks. These include sticky bandages, wooden tongue depressors, hospital linens, rooms with negative pressure, water leaks, poor air filtration, unsterilized medical equipment, and even the design of the building itself. Additionally, injuries caused by natural disasters have been associated with outbreaks that start in the community.



Drugs used in Mucormycosis:

Drugs like-

1] Amphotericin B.
2] Posaconazole
3] Isavucanazole
4] Fluconazole
5] Voriconazole
6] Echinocandins

These medications are administered orally or intravenously.

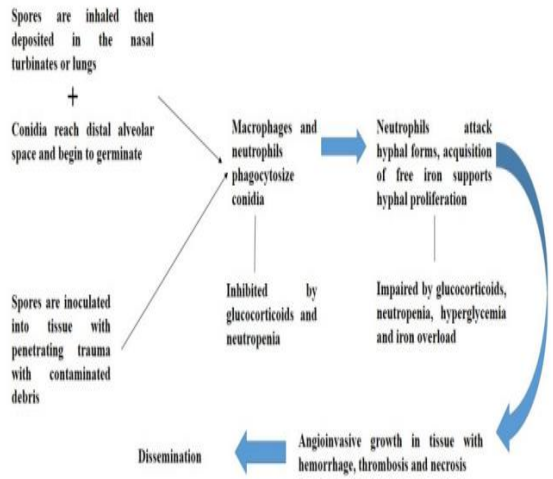
Mechanism of Mucormycosis:

Mucorales spores can trigger an inflammatory response even in healthy individuals, but they pose a greater risk to those with weakened immune systems, particularly those with conditions affecting their phagocytes (the cells that help fight infections). Infections often begin after skin

or soft tissue infections and are sometimes linked to illicit drug use.

These fungi grow aggressively due to several traits. They can tolerate high temperatures, grow quickly, and adapt their cell walls to survive in difficult environments. A key factor in the severity of mucormycosis is iron. People with too much iron in their bodies are especially vulnerable to these infections.

Because iron is so important for the growth of Mucorales, treatments that lower available iron levels could be helpful. New iron chelators (drugs that bind to iron) have shown promise in animal studies. However, these treatments might not work well for patients with low white blood cell counts.



Pathogenesis and host defence:

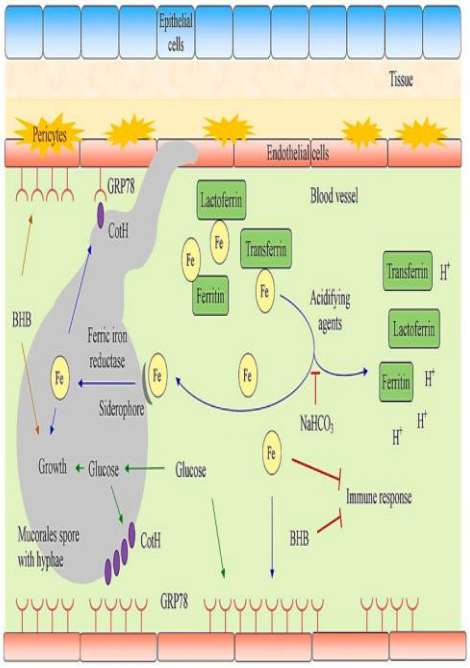
The genome of Rhizopus arrhizus is highly repetitive and contains many mobile genetic elements, making up about 20% of its DNA. This repetition, along with past and recent gene duplication events, has led to an increase in genes that help with energy production, cell growth, signaling, and virulence factors that allow the fungus to invade host tissues.

Mucormycosis, the infection caused by this fungus, is characterized by its ability to invade blood vessels (angioinvasion) with minimal inflammation. This invasion can block blood flow, causing tissue death (necrosis) in nearby areas. When tissues die, it prevents immune cells from gathering at the infection site, allowing the fungus to spread to other organs. Interactions between the fungus and the cells lining blood vessels are critical to how the infection develops. Both live and dead Rhizopus can damage these endothelial cells, allowing the fungus to attach and be engulfed by immune cells.

Researchers have identified a receptor called glucose-regulated protein 78 (GRP78) on endothelial cells that specifically interacts with Rhizopus. High levels of glucose and iron, often found in patients with diabetic ketoacidosis (DKA), increase GRP78 expression, which aids the fungus in invading tissues. Another protein from the fungus, called CotH, also plays a significant role in this process.

To establish an infection, the fungal spores must evade the host's immune system and begin growing. Interestingly, people with healthy immune systems don't always develop mucormycosis, even though the spores can easily enter through the respiratory tract.

The body has several defenses against fungal infections, including physical barriers and immune responses aimed at limiting iron availability, which fungi need to thrive. The body uses proteins that bind iron to keep it out of reach of the fungi. In response to low iron levels, fungi produce proteins that help them absorb as much iron as possible from their environment. Rhizopus produces a specific iron-binding molecule called rhizoferrin.



Patients with DKA often have high levels of free iron in their blood, which supports the growth of R. arrhizus in acidic conditions.

Immune cells, like macrophages and neutrophils, play a crucial role in fighting off the infection. Macrophages can engulf fungal spores, while neutrophils are attracted to the area and help destroy the fungi using various methods, including producing reactive oxygen species and releasing signaling molecules to trigger an immune response.

Additionally, Rhizopus hyphae can activate toll-like receptors (TLRs) on immune cells, which help recognize the fungus and initiate the immune response. Platelets also contribute

by attaching to the fungal structures, preventing their growth and helping activate other immune cells. Natural killer (NK) cells can also attack R. arrhizus and elp damage it

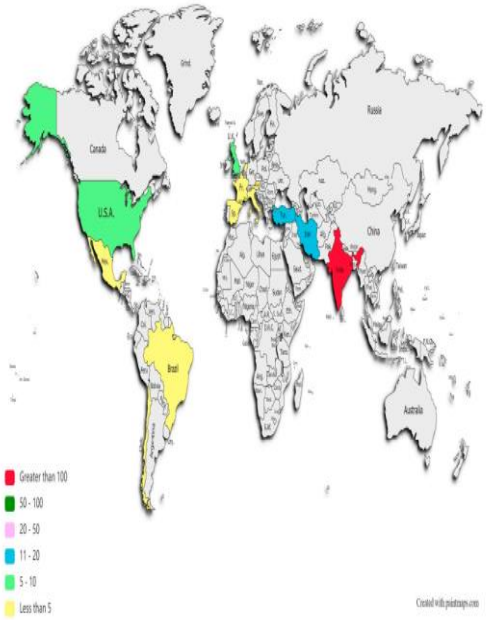
further. Overall, the interaction between the fungus and the immune system is complex and crucial for understanding how mucormycosis develops and progresses.

Geographical distribution of Mucormycosis:

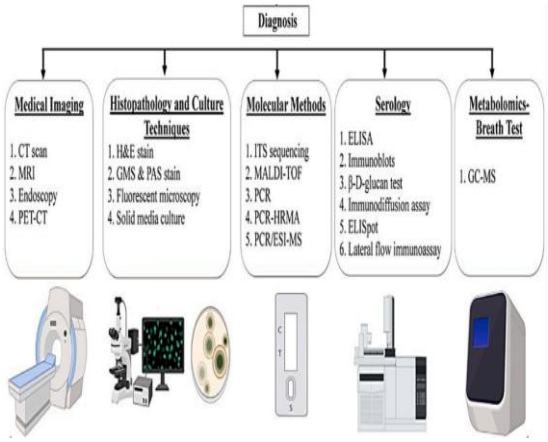
A study by Song et al. highlighted that critically ill patients in ICUs, especially those on mechanical ventilation, are vulnerable to various fungal infections, including during SARS outbreaks. While other fungal infections were noted, it wasn't until May 2020 that mucormycosis cases were confirmed.

A post-mortem study conducted in the UK from March to April 2020 identified a patient with disseminated mucormycosis through biopsy, PCR, and DNA extraction. Following that, multiple cases of mucormycosis co-infections in patients with ongoing or recovering COVID-19 have been reported. As the second and third waves of COVID-19 hit, a global syndemic of mucormycosis emerged, affecting many countries, including India, Pakistan, France, Iran, and several others.

By early June 2021, India was particularly hard-hit, with over 20,000 cases of COVID-19-associated mucormycosis (CAM), making it the worst-affected country. A systematic review found a total of 201 reported cases of CAM and 70 deaths across 13 countries. India had the highest number of cases at 138, followed by Iran with 18, and Turkey with 12. The review also included a supplementary table that detailed active or post-mortem CAM cases by country.



Diagnosis of Mucormycosis:



1]Medical imaging: Medical imaging techniques like CT scans, MRIs, and endoscopy play a crucial role in assessing the extent of mucormycosis infections. For patients suspected of having pulmonary mucormycosis, a CT scan is recommended to identify the "reversed halo sign," which appears as a ground-glass opacity surrounded by a ring of consolidation—a key indicator of the infection.

CT pulmonary angiograms can be used to check for any vessel blockages in the lungs. If rhino-orbital-cerebral mucormycosis is suspected, cranial CT or MRI scans are advised. MRI is preferred over CT for detecting any invasion into the eyes or brain due to its higher sensitivity.

Once mucormycosis is confirmed, regular imaging of the brain, chest, or abdomen is essential to monitor the infection's progression or spread. In the future, PET/CT scans using a radioactive glucose marker may also be utilized for improved sensitivity in detecting the disease.

2]Histology and Cultural Techniques: Mucormycosis is often suspected based on direct microscopic analysis of samples. To improve visibility of the fungal hyphae, fluorescent dyes like blankophor and calcofluor white are used alongside potassium hydroxide (KOH). The diagnosis is confirmed by observing the typical characteristics of the hyphae using stains like hematoxylin and eosin, periodic acid-Schiff, or Grocott-Gomori's methenamine silver stain.

When examining tissue samples, it's important to note that the processing can sometimes create pseudo-septa or distort the typical 45-degree branching angle. A key feature for identifying mucormycosis is the wide, irregularly shaped hyphae.

In acute infections, you may see signs like tissue death (coagulative necrosis), blood vessel invasion, and neutrophil infiltration. In chronic cases, you might observe a type of inflammation called pyogranulomatous, and hyphae may appear surrounded by a specific

immune response known as the Splendore-Hoeppli phenomenon. However, these lesions can be quite nonspecific, making it easy to confuse mucormycosis with Aspergillosis.

To address these challenges, immunohistochemistry techniques using monoclonal antibodies can help differentiate between mucormycosis and

Aspergillosis. For preliminary identification of fungi at the genus and species levels, solid media culture is useful, followed by both macroscopic and microscopic assessments for a more accurate diagnosis and antifungal susceptibility testing.

3]Molecular Methods: For accurately identifying fungi at the genus and species levels, sensitive molecular methods are essential. Molecular analysis is preferred over traditional histological methods because it is more reliable.

One commonly used method is internal transcribed spacer (ITS) sequencing, which is favored over Matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) due to some of its limitations. There are several advanced and specific techniques available for rapid pathogen detection, including nested PCR, restriction fragment length polymorphism (RFLP) coupled with nested PCR, quantitative PCR (qPCR), high-resolution melting analysis (HRMA), and PCR combined with electrospray ionization mass spectrometry (PCR/ESI-MS).

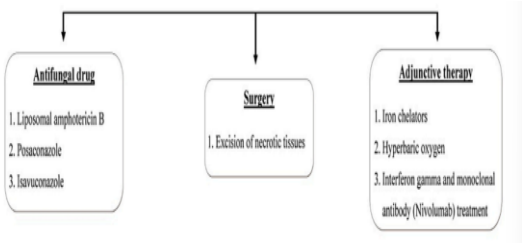
These methods primarily target specific regions of the fungal DNA, such as the 18S and 28S ribosomal RNA genes, the cytochrome b gene, a mitochondrial gene called rnl, the CotH gene, and the ITS region. These targets are particularly relevant for identifying fungi like Rhizopus arrhizus, various Mucor species, and Rhizopus microsporus.

4]Serology: To detect mucormycosis infections, several serological techniques are commonly used, including ELISA (enzyme-linked immunosorbent assay), immunoblots, the β-D-glucan test, and immunodiffusion tests. One specific method, the enzyme-linked immunospot (ELISpot) assay, can identify Mucorales-specific T-cells.

In a sandwich ELISA test, a monoclonal antibody called 2DA6 is highly reactive with a component of the Mucor cell wall known as fucomannan. However, a lateral flow immunoassay that detects fucomannan is more convenient than the traditional ELISA and could potentially be used for quick testing at the point of care.

5]Metabolomics Breath Test: The metabolomics breath test is a method that detects volatile organic compounds in the breath of patients with mucormycosis. Koshy and colleagues studied the breath profiles of different fungi causing invasive mucormycosis, including Rhizopus arrhizus var. delmar and Rhizopus microsporus, using gas chromatography-mass spectrometry (GC-MS). They found that each of these fungal species has a unique breath profile, suggesting that this test could serve as a non-invasive diagnostic tool for invasive mucormycosis. Such real-time breath tests could enable large-scale screening, allowing for earlier detection and treatment of mucormycosis before it progresses to more severe stages.

Treatment of Mucormycosis:



1]Antifungal Drugs: Amphotericin B is the primary treatment for mucormycosis and can greatly improve patient outcomes. A study involving 70 patients showed that delaying amphotericin B treatment by just six days after diagnosis nearly doubled the risk of death within 12 weeks (83% versus 49%).

Treatment with amphotericin B should continue until the patient shows clear clinical improvement, which typically takes a few weeks. The lipid formulation of intravenous amphotericin B is usually preferred over the cheaper and more toxic deoxycholate form. It's also important to monitor and replenish metabolites after amphotericin therapy. A study of 368 patients found that routine electrolyte replenishment and IV saline hydration helped reduce metabolic issues and kidney complications related to amphotericin B toxicity. However, it's worth noting that amphotericin B is not effective against Cunninghamella and Apophysomyces species.

For patients with kidney problems, triazoles like posaconazole and isavuconazole are recommended. These drugs work by inhibiting ergosterol synthesis in fungal cell membranes and are effective against mucormycosis. They come in both oral and intravenous forms and can be used for salvage therapy or as a step-down treatment for patients who can tolerate amphotericin B. Currently, there are no main guidelines recommending fungal combination therapy, but larger trials are needed to evaluate its effectiveness.

Isavuconazole is a newer drug approved for mucormycosis in the U.S. and Europe and may become a standard treatment for invasive fungal infections. It's available in both oral and IV forms and is an improvement over voriconazole, as it lacks the cyclodextrins that cause kidney toxicity. Isavuconazole also has a longer half-life, allowing for once-daily dosing. Studies have shown no significant difference in mortality rates between patients treated with amphotericin B and those treated with isavuconazole.

In mouse models, combining caspofungin with lipid formulations of amphotericin B has shown better survival rates compared to monotherapy or placebo. Similarly, using liposomal amphotericin B with either micafungin or anidulafungin has led to better outcomes in cases of disseminated mucormycosis. If considering this combination therapy, it should be administered at doses approved by the U.S. Food and Drug Administration (FDA).

2]Surgery: Angioinvasion and blood vessel thrombosis can limit how effectively antifungal drugs reach the infection site. Therefore, patients with even a slight suspicion of mucormycosis should be prepared for surgery as a priority. Surgically removing infected tissue has been shown to significantly reduce mortality rates.

An MRI or CT-guided endoscopic approach is recommended to remove affected tissue, especially in cases where the infection has rapidly spread to the eye area (within 72 hours). In such situations, orbital exenteration (removal of the eye) and aggressive debridement of the paranasal sinuses may be necessary. After surgery, patients should continue receiving intravenous amphotericin B, followed by step-down therapy. For cases that do not respond to initial treatments, triazoles can be used.

In patients who are severely immunocompromised, the first step should be to address the underlying immunosuppression before starting antifungal treatment. Follow-up improvements should be monitored with repeat imaging and careful management.

3]Adjunctive Therapy: In patients with blood disorders, efforts should be made to address neutropenia, such as using growth factors or white blood cell infusions. For

those with immunosuppression from corticosteroids, like autoimmune disorder patients, it's advisable to reduce or switch their medications to non-steroidal options. HIV/AIDS patients should start antiretroviral therapy to boost their immune response. Managing blood sugar levels is crucial for individuals with uncontrolled diabetes or ketoacidosis. While more research is needed, iron chelation therapy could be beneficial for diabetic patients, particularly those with ketoacidosis, as it helps remove excess iron.

Managing other existing health issues is also essential. Hyperbaric oxygen (HBO) therapy can be a helpful addition to other treatments. The high oxygen levels can enhance how well neutrophils function, improve the effectiveness of amphotericin B (AMB), correct acidosis, and inhibit fungal growth by preventing spore germination. HBO therapy is recommended alongside surgery and antifungal treatments for mucormycosis.

Because these infections can be hard to detect, delays in starting antifungal therapy can lead to higher death rates. Currently, blood cultures are the most common diagnostic method, but they have low sensitivity and can take a long time for results. Using faster and more accurate tests like Enzyme-Linked Immunosorbent Assays (ELISA) alongside cultures can help identify fungal species and monitor drug resistance. If there's any suspicion of a fungal infection, it's important to start antifungal treatment immediately.

Prevention of Mucormycosis

- Use masks if you are visiting dusty construction sites and crowded place
- Daily change the mask either it should be new or has dried up in sunlight for about 2-3 days because mask provides optimum temperature, humidity and darkness for fungal growth
- Wear shoes, long trousers, long sleeve shirts and gloves while handling soil (gardening), moss or manure
- Maintain personal hygiene, including thorough scrub bath

Do's:

- Control hyperglycemia
- Monitor blood glucose level post-COVID-19 discharge and also in diabetics
- Use steroid judiciously – correct timing, correct dose and duration
- Use clean, sterile water for humidifiers during oxygen
- Use antibiotics/antifungals judiciously

Don'ts:

- Do not miss warning signs and symptoms
- Do not consider all the cases with blocked nose as cases of bacterial sinusitis, particularly in the context of immunosuppression and/or COVID-19 patients on immunomodulators
- Do not hesitate to seek aggressive investigations, as appropriate (KOH staining & microscopy, culture, MALDITOF), for detecting fungal etiology
- Do not lose crucial time to initiate treatment for mucormycosis

Conclusion:

In the past months of 2021, there was a significant increase in global cases of mucormycosis, with thousands of infections reported. The exact cause of this surge is still unclear. There haven't been enough population-based studies to determine the exact numbers of cases from previous years and the recent rise.

The second wave of the COVID-19 pandemic, particularly with the emergence of new variants, has added to the complexity of the situation, as the world is now facing two dangerous pathogens. In India, alongside the concerns about "black fungus," cases of "white fungus" and "yellow fungus" have also been reported. Health officials found all three types of pathogens in a 45-year-old patient in Ghaziabad, India. While some have identified "white fungus" as Aspergillus flavus, others believe these names are just colloquial terms for different patterns of mucormycosis infections.

It's clear that fungal infections are on the rise. According to the Centers for Disease Control and Prevention (CDC), conditions like Aspergillosis, Candidiasis, multidrug-resistant Candida auris infections, and Pneumocystis pneumonia are all caused by fungi that affect immunocompromised individuals. The rushed and improper use of antifungal drugs to address the current mucormycosis outbreak may lead to increased antifungal resistance, which could further escalate fungal infections.

There's concern that if effective measures are not taken, we might see the rise of more fungal species as we deal with current and future waves of the COVID-19 pandemic. The delta variant of SARS-CoV-2, which is prevalent in India, is particularly worrisome.

To better understand these co-infections during respiratory viral outbreaks, it's crucial to conduct thorough research, drawing insights from previous epidemics like influenza, SARS, and MERS. Additionally, enhancing genomic studies to identify host factors that make people more susceptible to serious infections like mucormycosis would be extremely beneficial for public health, both in India and globally.

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