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Mucormycosis

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ABSTRACT

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Mucormycosis is sometimes called Zygomycosis. It is a rare but serious fungal infection caused by a group of molds called mucormycetes. These fungi are ubiquitous in the environment, inhabiting soil especially decaying organic matter, such as leaves, compost piles, or rotten wood. They are more common in soil than in air, and in summer and fall than in winter or spring.

Keywords: Mucor, Mucormycosis, Black fungus, Covid, Post-Covid

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MORPHOLOGY OF MUCORMYCOSIS

Mucormycosis is sometimes called Zygomycosis. It is a rare but serious fungal infection caused by a group of molds called mucormycetes. These fungi are ubiquitous in the environment, inhabiting soil especially decaying organic matter, such as leaves, compost piles, or rotten wood **(Figure 1)**. They are more common in soil than in air, and in summer and fall than in winter or spring.[1] There are two orders of Zygomycetes: Mucorales and Entomophthorales. The majority of human illness are caused by the organisms in Mucorales.[2] The most common types that cause mucormycosis are Rhizopus species and Mucor species followed by rarer organisms Rhizomucor species, Syncephalastrum species, Cunninghamella bertholletiae, Lichtheimia (formerly Absidia), Saksenaea, and Rhizomucor.[1]

It is important to realize that Mucormycosis occurs only rarely in immunocompetent hosts. The spores from these molds are transmitted by (a) inhalation, (b) percutaneous routes, or (c) ingestion of spores. Human Mucormycosis generally occurs in immunocompromised hosts as an opportunistic infections. Mucormycosis causes angioinvasive disease, often leading to thrombosis, infarction of involved tissues, and tissue destruction mediated by a number of fungal proteases, lipases, and mycotoxins. If the diagnosis is not made early, disseminated disease results.[2] The infection is relentlessly progressive and results in death unless treatment with a combination of surgical debridement and antifungal therapy is initiated promptly.

PATHOPHYSIOLOGY OF MUCORMYCOSIS

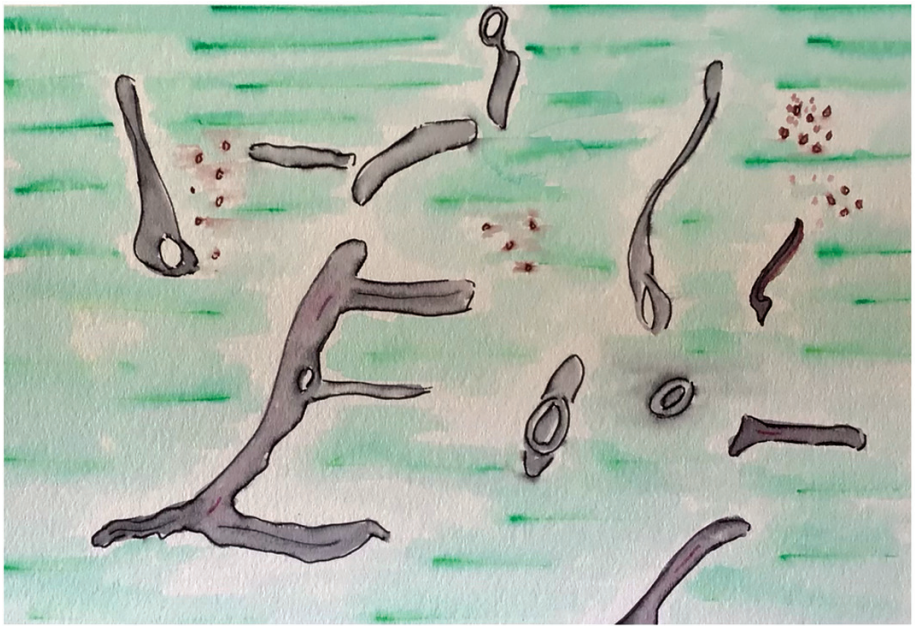

Figure 1. **Artistic depiction of GMS (Gomori Methenamine Silver) stain showing irregular, large, ribbon shaped and unbranched hyphae of Mucormycosis species. M.D**

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To cause disease in humans, the agents of Mucormycosis must scavenge from the host sufficient iron for growth, evade host phagocytic defense mechanisms, and then disseminate by blood vessels. The role of iron is particularly important in Mucormycosis. In a normal host, primary defense mechanisms against Mucormycosis include the sequestration of iron in serum by specialized iron-binding prot eins, presence of circulating neutrophils and tissue macrophages and lastly viable endothelial cells, which regulate vascular tone and permeability. Acting together these normal host mechanisms prevent establishment of infection in tissue and subsequent endovascular invasion.

In susceptible hosts, normal defense mechanisms break down. Patients in diabetic ketoacidosis (DKA), have an acidic pH in the serum that causes dissociation of free iron from sequestering proteins, such as transferrin. This release of free iron allows rapid fungal growth. Defects in phagocytic defense mechanisms such as a deficiency in cell number (neutropenia) or functional defects caused by corticosteroids or the hyperglycemia and acidosis of diabetic ketoacidosis, allow proliferation of the fungus. Finally, adherence to and damage of endothelial cells by the fungus allows fungal angioinvasion and vessel thrombosis and subsequent tissue necrosis and dissemination of the fungal infection.[3]

RISK FACTORS FOR INFECTION

Host risk factors for Mucormycosis include diabetes mellitus, neutropenia, sustained immunosuppressive therapy, chronic prednisone use, iron chelation therapy, broad-spectrum antibiotic use, severe malnutrition, and breakdown in the integrity of skin barrier brought about by trauma, surgical wounds, needle sticks, or burns **(Table 1, Table 2)**. The disease manifestations reflects the mode of transmission, with rhinocerebral and pulmonary diseases being the most common manifestations. Cutaneous, gastrointestinal, renal and allergic diseases are also seen.[2] CNS spread is usually a sign of dissemination and can herald a poor prognosis. It is important to educate patients that Mucormycosis cannot be spread between people.

Table 1, below illustrates the common risk factors. Hospitalized patients have further risks arising from contaminated adhesives and tapes, wooden tongue depressors used to secure IV access sites or in mixing of oral feeds, ostomy bags, contaminated nasal packing, hospital linen, water leaks, ongoing building construction, and infected vascular access catheters.[1,4] Therefore good infection control practices are paramount to prevention of hospital acquired Mucormycosis.

Most cases of Mucormycosis are sporadic with rare hospital acquired infections.. Community-onset outbreaks have been associated with trauma sustained from natural disasters such as flooding, tornadoes and volcanic eruptions. The ongoing epidemic of Mucormycosis seen in India with COVID-19 since April 2021 is the largest documented outbreak with an unclear etiology at this time. In the United States, a Population-based incidence estimates for mucormycosis obtained from laboratory surveillance in the San Francisco Bay Area during 1992–1993 suggested a yearly rate of 1.7 cases per 1 million population.[10] For a better understanding of this epidemic, it will help to review the risk factors for Mucormycosis in patients with hematologic malignancies. **Table 2,** is adopted from the work of Kontoyiannis et al.[5]

CLINICAL FINDINGS OF MUCORMYCOSIS

There are five major clinical forms of Mucormycosis; of these, rhinocerebral and pulmonary infections are the most common.[1] The most common site of spread is the brain, but the spleen, heart, skin, and other organs

Table 1. Identified risk factors for Mucormycosis.[1]

Diabetes mellitus, especially with diabetic ketoacidosis
Neutropenia
Cancer, especially hematologic malignancies
Organ transplantation, including hematopoietic stem cells
Long term corticosteroid use
Injection drug use
Iron overload conditions such as hemochromatosis
Skin breakdown from trauma, surgery, burns
Prematurity or low birth weight

Table 2. Predisposing risk factors for Mucormycosis in patients with hematologic malignancies and or stem cell transplantation

Prolonged (> 3 wk) and severe (ANC < 200) neutropenia.
Monocytopenia (< 100 mm3).
Colonization by mucormycetes or heavy environmental exposure.
Previous exposure to Aspergillus-active antifungal agents, especially voriconazole.
Prolonged (> 3 wk) high-dose systemic corticosteroids (eg, prednisone or equivalent of > 1 mg/kg/d)
Prolonged hyperglycemia (fasting serum glucose > 200 mg/dL), corticosteroid- associated hyperglycemia and diabetes mellitus
Iron overload
Relapsed leukemia
High-risk SCT (eg, matched-unrelated donor SCT, cord blood SCT)
Severe GVHD and its treatment (especially corticosteroids)

ANC = Absolute Neutrophil Count, SCT = Stem Cell Transplant.

Table 3. Clinical manifestations of Mucormycosis
Rhinocerebral
Pulmonary
Cutaneous
Gastrointestinal
Disseminated

can also be affected. In immunocompromised patients, the main route of infection appears to be via inhalation of sporangiospores causing pulmonary infection.[6] Other ways in which Mucormycosis can be acquired is through ingestion and per cutaneous inoculation of the skin

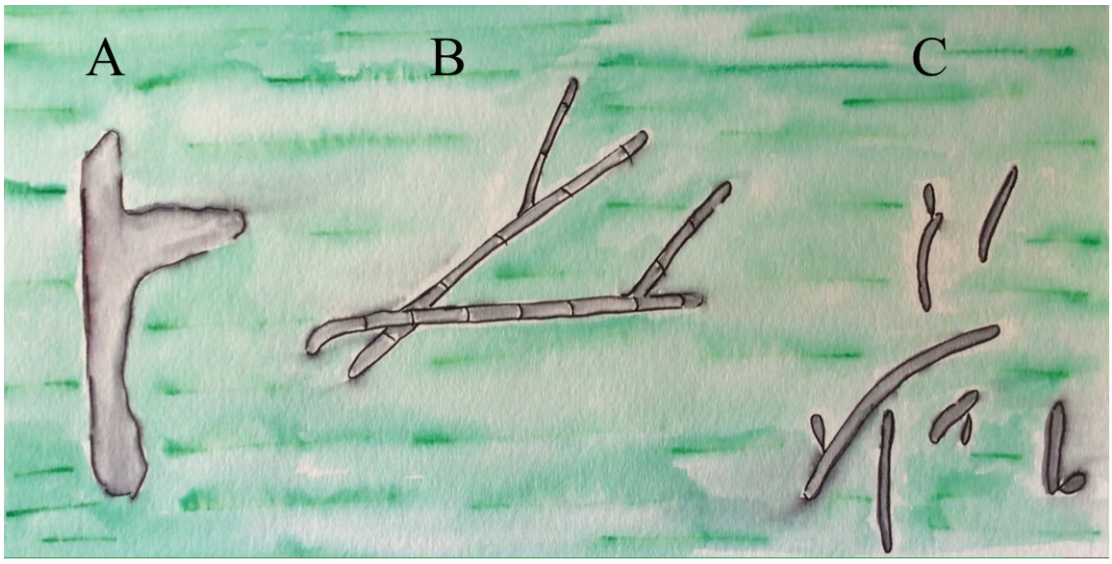
Rhinocerebral mucormycosis can present as a unilateral facial swelling, headache, nasal or sinus congestion or pain, and a serosanguinous nasal discharge that maybe accompanied by fever. As it disseminates, ptosis, proptosis, loss of extraocular muscle function, and vision disturbance may occur **(Table 3)**. Examination can reveal necrotic black lesions on the hard palate or nasal turbinate, and or drainage of black purulence from the affected areas.

Cutaneous mucormycosis can be primary or secondary. Primary infection can happen in immunocompetent hosts as a result of direct inoculation into disrupted skin such as in patients with burns or other forms of local skin trauma, like those suffered in victims of hurricanes or tsunamis. Disease usually presents with purulence, abscess formation, tissue swelling, and necrosis. The skin lesions can appear red and indurated and progress to black eschars. Secondary infection occurs when the pathogen spreads hematogenously usually in immunosuppressed hosts with a similar presentation as primary infection, though these hosts may not produce purulence. The cellulitic lesions can be erythematous, indurated, painful and then progress to an ulcer covered with a black eschar.[1]

Pulmonary mucormycosis symptoms are generally non-specific and may include fever, cough, chest pain, and dyspnea. Later as tissue necrosis occurs, hemoptysis may happen with cavitation noted late on imaging studies. Gastrointestinal mucormycosis is less common and is believed to result from ingestion of the organism. It typically occurs in malnourished patients or premature infants. The stomach, colon, and ileum are most commonly affected. Non-specific abdominal pain and distension, nausea, and vomiting are the most common symptoms, and gastrointestinal bleeding can occur. Disseminated mucormycosis can follow any of the forms of mucormycosis described above but is usually described in immunocompromised patients with a pulmonary infection.[1]

DIAGNOSIS OF MUCORMYCOSIS

It is important to identify Mucormycosis species (Mucormycetes) early on in the disease process so that appropriate treatment decisions can be made. A definitive diagnosis of mucormycosis requires histopathological evidence or positive culture from a specimen taken from the site of infection. Specimens from sterile body sites offer stronger evidence of invasive infection compared to non sterile areas such as sputum that may indicate colonization.



A = Mucormycosis species, B = Aspergillus species and C = Candida species

Figure 2. **Highlights the main areas of difference between Mucormycetes, Aspergillus and Candida species**

On a GMS stain, Mucormycetes appear as irregular, broad ribbons with 90 degree branching noted, while Aspergillus species appear as regular, narrow filaments with septum and branch at an acute angle **(Figure 2)**. Candida species on the other hand have pseudo hyphae and blastoconidia, with budding present.

Despite all of the above, Mucormycetes may be difficult to differentiate from other filamentous fungi in tissue even for experienced pathologists. To increase the yield of microbiological diagnosis, it is often helpful to not grind the tissues taken but make thin slices. No commercially available routine serologic tests for mucormycetes exist. DNA-based techniques for detection though promising are not fully standardized nor commercially available.[1]

RADIOGRAPHIC FINDINGS IN MUCORMYCOSIS

It should be noted, that it is difficult to make a diagnosis between Invasive Pulmonary Aspergillosis and Pulmonary Mucormycosis based on radiographic imaging studies. Definitive diagnosis requires a biopsy with cultures and pathology. In Pulmonary Mucormycosis the most common initial CT pattern reported was consolidation and nodule/mass with a Halo sign. As the disease progresses, with central necrosis occurring, a clear ring of consolidation forms giving rise to the "reverse halo sign". As necrosis continues, it leads to the "air crescent" sign developing, an indication usually of late stage disease.[7] Radiology plays a limited role in the diagnosis.

TREATMENT OF MUCORMYCOSIS

Early recognition, diagnosis, and prompt administration of appropriate antifungal treatment are critical for improving outcomes. Mucormycosis is a life threatening condition. The overall prognosis depends on the rapidity of diagnosis and institution of appropriate treatment, the site of infection, the patient's underlying conditions and the degree of immunosuppression. The overall mortality rate is estimated to be approximately 50%, though early identification and treatment can lead to improved outcomes.

Not all antifungal agents work against Mucormycetes. Neither Fluconazole nor Voriconazole have any activity against Mucormycetes and should not be used. In fact, there is concern that pre-exposure to voriconazole is associated with an increased incidence of mucormycosis in some patients.[8] Amphotericin B, posaconazole, and isavuconazole have activity against most mucormycetes. Lipid formulations of amphotericin B are often used as first-line treatment as they can be less nephrotoxic. One must bear in mind, that these antifungal medications are extremely expensive and are often required for weeks to months. In addition, these patients need extensive surgical debridement or resection of infected tissue particularly for rhinocerebral, cutaneous, and gastrointestinal infections. Even then mortality remains disproportionately high.

When ever possible, control of the underlying immunocompromising condition should be attempted. The efficacy of adjuvant treatments such as hyperbaric oxygen therapy is uncertain at best and have been useful in limited situations.[9]

END NOTE

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Conflict of Interest: None declared

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