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Review Article on Advances in Understanding and Managing Mucormycosis: Risk Factors, Clinical Presentations, and Treatment Strategies

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A B S T R A C T

Mucormycosis is a serious fungal infection caused by Mucorales fungi, particularly Rhizopus oryzae, which can impact various organs in the body. While these fungi are commonly found in the environment and pose no threat to individuals with a healthy immune system, people with compromised immunity, such as those with uncontrolled diabetes, HIV/AIDS, or who have undergone organ transplantation, are susceptible to severe fungal infections. This review article presents a summary of the risk factors, clinical presentations, and treatment options for Mucormycosis.

There are regional differences in risk factors, with diabetes mellitus being the most prevalent risk factor globally, particularly in Asia and Africa. Hematologic malignancies and solid organ transplantation also pose significant risks. Interestingly, some patients diagnosed with Mucormycosis do not have any identifiable predisposing conditions. In recent times, there has been a rise in Mucormycosis cases worldwide, particularly in India, among individuals with COVID-19. The favorable conditions created by COVID-19, including low oxygen levels, high glucose levels, and immune suppression, contribute to the growth of Mucorales spores.

Early diagnosis and prompt treatment are vital for managing Mucormycosis. The primary treatment approach involves early initiation of therapy, surgical removal of infected tissue, and antifungal treatment. The drug of choice is Amphotericin B, followed by triazole antifungals like posaconazole and isavuconazole. Liposomal amphotericin B is preferred due to its higher effectiveness and lower toxicity. It is important to regularly monitor kidney function during treatment. Surgical intervention is recommended for localized disease and has shown better outcomes compared to treatment with antifungal drugs alone.

In conclusion, Mucormycosis is a significant concern, particularly in individuals with compromised immune systems. Identifying risk factors, recognizing clinical presentations, and employing appropriate treatment strategies are crucial for effectively managing this fungal infection. Further research and increased awareness are necessary to improve early diagnosis, optimize treatment outcomes, and reduce the impact of Mucormycosis on affected individuals.

Keywords: Mucormycosis, covid-19, immunocompromised.

I. Introduction

Mucormycosis, caused by fungi from the Mucorales order, is an infection where Rhizopus oryzae is the predominant organism, accounting for 70% of cases (1). Mucorales fungi, a part of the zygomycete family, are widely found in the environment but do not cause harm to individuals with a healthy immune system. The infection typically occurs through inhalation of spores, which then spread to the paranasal sinuses and lungs. Immunocompromised patients, such as those with uncontrolled diabetes, diabetic ketoacidosis, HIV/AIDS, lacerating wounds, cancer, or organ transplantation, are susceptible to severe fungal infections.

Mucormycosis is most commonly observed in highly immunocompromised individuals in developing countries, as supported by studies (Nasa et al., 2017; Wang et al., 2018). In developed economies, mucormycosis is frequently seen in patients with poorly managed diabetes and those who have experienced trauma (Petrikkos et al., 2012a, b). The clinical presentations of mucormycosis are categorized based on the affected anatomical sites, including rhino-orbital-cerebral (ROCM), pulmonary, gastrointestinal, cutaneous, renal, and disseminated mucormycosis. In India, uncontrolled diabetes mellitus is the most prevalent underlying condition associated with mucormycosis, in contrast to developed countries where it is more commonly observed in patients with hematological malignancies or solid organ transplants(3).

Mucormycosis encompasses a group of fungal infections caused by Mucorales, affecting various organs such as the skin, paranasal sinuses, orbits, brain, lungs, and gastrointestinal tract. The risk factors for mucormycosis include uncontrolled diabetes mellitus, hematologic malignancy (particularly acute leukemia), stem cell transplantation, solid organ transplantation, neutropenia, deferoxamine therapy, and corticosteroid use. A systematic literature review covering the period from 2000 to 2017, involving 851 patients with different forms of mucormycosis, revealed geographical variations in risk factors.

Globally, diabetes mellitus was the most common risk factor, affecting 40% of patients, with higher prevalence in Asia (46%) and Africa (75%) compared to Western countries (36%). Hematologic malignancy was the next most common risk factor (32%), followed by solid organ transplant (14%). Notably, 18% of patients with all types of mucormycosis had no identifiable predisposing condition (4).

II. Risk factors associated with mucormycosis

Mucormycosis, a fungal infection, is a significant concern in the Indian population. It is commonly observed in individuals with underlying conditions such as diabetes mellitus (the most common underlying disease), haematological malignancies, and solid-organ transplants. Interestingly, mucormycosis can also occur in immunocompetent individuals. A lack of regular health check-ups in India has resulted in the identification of diabetes in a significant number of mucormycosis patients, including 43% in North India, 40% in Western India, and 24% in South India (3). Clinical and experimental data have demonstrated that individuals with impaired phagocytic function, such as severely neutropenic patients, are at a higher risk of developing mucormycosis (1).

Additionally, systemic corticosteroid treatment, while reducing mortality in severe cases, can also predispose patients to secondary fungal infections. Despite the primary focus on COVID-19-associated pulmonary aspergillosis in the literature, other fungal superinfections like Candida infections, rare mold infections (fusariosis), and COVID-19-associated mucormycosis are likely underreported. The risk factors associated with mucormycosis include uncontrolled diabetes, neutropenia, haematological malignancies, organ transplantation, trauma, burns, and the use of immunosuppressants such as corticosteroids (5). Both Aspergillus and Candida are reported as the main fungal pathogens for co-infection in COVID-19 patients. In recent times, there has been an increasing number of mucormycosis cases reported worldwide, particularly in India, among individuals with COVID-19. The primary factors facilitating the germination of Mucorales spores in COVID-19 patients include a favorable environment characterized by low oxygen levels (hypoxia), high glucose levels (diabetes, new-onset hyperglycemia, steroid-induced hyperglycemia), an acidic medium (metabolic acidosis, diabetic ketoacidosis [DKA]), high iron levels (increased ferritins), and decreased phagocytic activity of white blood cells due to immunosuppression caused by SARS-CoV-2 infection, steroid use, or underlying comorbidities. Prolonged hospitalization is also a shared risk factor.

The progression of mucormycosis is linked to various factors, including poorly regulated type 1 diabetes, haematological malignancies with neutropenia, hematopoietic stem cell transplantation, solid organ transplants, immunosuppression or chemotherapy, rheumatic or autoimmune disorders, HIV infection, peritoneal dialysis, iron overload states, malnutrition, trauma, burns, and prior receipt of certain medications like voriconazole (Dimaka et al. 2014; Husain et al. 2017; Kennedy et al. 2016; Kontoyiannis et al. 2005; Lanternier et al. 2012a, b; Moreira et al. 2016a, b; Pana et al. 2016). While mucormycosis appears to be protective in immunocompetent individuals (Radner et al. 1995), infections have been identified after soft tissue damage, or localized cutaneous, rhino-orbital, cutaneous, and disseminated infections in some cases (Blauwkamp et al. 2019; Tribble et al. 2018) (7).

III. Clinical presentation

Clinical presentations of mucormycosis vary depending on the anatomical sites affected. The following are common clinical manifestations:

1. Rhino-Orbital-Cerebral Mucormycosis (ROCM): Predominantly affecting the nose, sinuses, eyes, and brain, ROCM presents with symptoms such as nasal congestion, facial pain, eye bulging, eye muscle paralysis, black necrotic tissue in the nasal area, and signs of intracranial involvement such as headaches, altered mental status, or seizures.

2. Pulmonary Mucormycosis: Involving the lungs, pulmonary mucormycosis presents with cough, shortness of breath, chest pain, coughing up blood, fever, and pleuritic chest pain. Radiographic findings may show lung nodules, consolidations, or cavitary lesions.

3. Gastrointestinal Mucormycosis: Affecting the gastrointestinal tract, particularly the stomach and intestines, gastrointestinal mucormycosis manifests as abdominal pain, gastrointestinal bleeding, diarrhea, nausea, vomiting, or signs of intestinal obstruction. Imaging studies may reveal bowel wall thickening or perforation.

4. Cutaneous Mucormycosis: Primarily impacting the skin and subcutaneous tissues, cutaneous mucormycosis presents with rapidly progressing skin lesions characterized by erythema, edema, necrosis, and the formation of black eschars. The lesions are often painful and tender.

5. Renal Mucormycosis: A rare form of mucormycosis, renal involvement leads to symptoms such as flank pain, blood in urine (hematuria), or signs of kidney dysfunction.

6. Disseminated Mucormycosis: This severe and life-threatening form occurs when the infection spreads to multiple organs or systems. Patients experience fever, sepsis, multiple organ involvement, and rapidly deteriorating clinical conditions.

These clinical presentations provide valuable insights into the diverse manifestations of mucormycosis and aid in early diagnosis and management(9).

IV. Treatment

The treatment of mucormycosis involves early initiation of therapy, surgical debridement of infected tissue, antifungal therapy, and management of the underlying disease. The first-line drug of choice is Amphotericin B (AmB), with subsequent use of posaconazole and isavuconazole (3).

Due to the patient's current health condition, timely diagnosis and testing are often challenging, increasing the risk of invasive mold infections. The high number of COVID-19 patients strains hospital resources, including diagnostics and surgeries. Optimal glycemic control during hospitalization, coupled with early initiation of liposomal amphotericin B treatment, improves outcomes in such patients. Systemic administration of liposomal amphotericin B is preferred due to its higher efficacy and lower toxicity, allowing for prolonged administration without side effects. Regular monitoring of renal function is necessary due to the potential nephrotoxicity of liposomal amphotericin B. As a second-line treatment, triazole antifungals such as posaconazole and isavuconazole are used. Isavuconazole, with its broad-spectrum action, is particularly effective in treating invasive mucormycosis (2).

Surgery is recommended for patients with localized disease and has shown better outcomes compared to antifungal therapy alone. Surgical options for localized disease include wedge resection, lobectomy, or pneumonectomy. Bilateral disease is less common but can be effectively managed with surgery for source control (8).

TABLE 1- TREATMENT FOR MUCORMYCOSIS

Antifungal agent	Dose	Duration
Posaconazole IV/tablet:	1×300 mg from day 2, 2×300 mg day 1 • Oral suspension: 2×400 mg/day or 4×200 mg/day	6 months
Amphotericin B (ABCL, AMB, LAMB) CNS participation: LAMB No CNS participation:	1 mg/100 g per day 0.5 mg/100 g per day LAMB	Usually 6–12 weeks
Isavuconazole IV or PO:	3×200 mg day 1, 1×200 mg/day from day 3	3 for 3 months

(1)

V. Conclusion

In conclusion, mucormycosis is a significant fungal infection caused by Mucorales fungi, predominantly Rhizopus oryzae. It primarily affects immunocompromised individuals, with uncontrolled diabetes being the most prevalent underlying condition in the Indian population. The infection can also occur in immunocompetent individuals, particularly in the presence of certain risk factors such as trauma, burns, and immunosuppressive therapies.

The clinical presentation of mucormycosis varies depending on the affected anatomical sites, including the rhino-orbital-cerebral, pulmonary, gastrointestinal, cutaneous, renal, and disseminated forms. Prompt initiation of therapy is crucial and involves a multidisciplinary approach, including surgical debridement, antifungal therapy, and management of the underlying disease. Amphotericin B is the first-line drug of choice, followed by posaconazole and isavuconazole. Liposomal amphotericin B is preferred due to its efficacy and lower toxicity. Regular monitoring of renal function is necessary due to potential nephrotoxicity.

Surgery is recommended for localized disease and can significantly improve outcomes compared to antifungal therapy alone. The increasing prevalence of mucormycosis, particularly in the context of COVID-19, highlights the importance of early diagnosis, proper management of underlying conditions, and optimization of healthcare resources. Further research is needed to enhance our understanding of the risk factors, pathogenesis, and treatment options for this serious fungal infection.

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