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Old Disease, New Faces; Mucormycosis in Post SARS Covid-19 Era: A Review

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Abstract

Mucormycosis is a severe yet uncommon angioinvasive fungal infection that progresses rapidly, making early diagnosis and treatment essential to reduce its high mortality and morbidity rates. The disease arises primarily from inhalation of filamentous (hyphal) fungal spores, particularly in immunocompromised individuals. This review highlights the etiopathogenesis of mucormycosis, the fatal consequences of rhino cerebral mucormycosis, its complex association with COVID-19, and the latest advances in diagnostic and therapeutic approaches.

Keywords: Mucormycosis, Oral manifestations, SARS COVID-19.

Introduction

Mucormycosis, also referred to as phycomycosis or "black fungus" (formerly known as zygomycosis), is a potentially lethal opportunistic fungal infection. It is caused by filamentous molds belonging to the orders Mucorales and Entomophthorales of the zygomycete family, which are capable of producing various types of infections [1].

These fungi are commonly found in soil, decaying organic matter (such as rotting fruits and vegetables), and animal manure. However, they rarely infect healthy

individuals and are not transmitted from person to person[2].

During the COVID-19 pandemic, a strong association was observed between mucormycosis and COVID-19, particularly in India, where cases increased markedly. This relationship is believed to be linked to immune suppression during COVID-19 infection and the widespread use of glucocorticoids in treatment [3].

Characterized by its rapid progression and high mortality rate, mucormycosis can manifest in various forms, including rhinocerebral, pulmonary, gastrointestinal, cutaneous, and disseminated infections. Prompt diagnosis and treatment are crucial to prevent severe morbidity and mortality. However, diagnosis is often delayed due to its nonspecific clinical presentation and limited awareness among healthcare professionals. This review aims to provide a comprehensive overview of mucormycosis, including its clinical manifestations, diagnosis, treatment options, and current challenges in management. By understanding this deadly fungal infection, healthcare professionals can improve patient outcomes and save lives [2].

Historic Background

The first case of mucormycosis was reported in 1885 by German pathologist Paltauf, who described it as Mycosis Mucorina[4] The 1980s and 1990s saw a rise in cases, particularly among immunocompromised individuals[3]. A study in France revealed an annual increase of 7.4% in incidence [5]. Globally, mucormycosis has been reported with indications of seasonal variation in Mucorales infections [6].

The rise has been perceived globally, but it is very high in the Asian continent. Though diabetes mellitus over shadow all other risk factors in Asia. Mucormycosis is found to be predisposed in co- morbidity or in the non-diabetic patients of COVID- 19 especially in those who were at high dosage of steroids for a longer period of time or on ventilator support. In a report, it is observed that among all the patients of COVID-19 associated mucormycosis (CAM) about 80.4-96.7%haddiabetes mellitus [4].

Etiopathogenesis

Mucorales invade deep tissues through ingestion, inhalation, or percutaneous inoculation of spores. In healthy individuals, the first line of defense—oxidative metabolites and cationic peptides—can typically neutralize these spores [7].

Risk Factors

The infection is more likely in individuals with uncontrolled diabetes mellitus, particularly ketoacidosis, steroid use, extremes of age, neutropenia (especially in hematological malignancies), AIDS, renal failure, organ or stem cell transplantation, iron overload, skin trauma, broad-spectrum antibiotic use, intravenous drug abuse, prolonged voriconazole prophylaxis for aspergillosis, malnutrition[7] .In diabetic patients, mucormycosis becomes highly destructive due to the increased availability of nutrients and reduced immune defense [8]. Proposed mechanisms include, low serum inhibitory activity against rhizopus species, enhanced iron availability in acidic conditions, reduced ability of pulmonary macrophages to inhibit rhizopus spore germination[9-11].

Rhizopus produces ketone reductase, which enables survival in high-glucose, acidic environments[11]. In patients with diabetic ketoacidosis (DKA), mucormycosis of all types can develop [11–14]. Neutrophils, essential in defense against Mucorales, have impaired function in DKA[13,16]. The acidic state accelerates fungal invasion[17], while free iron availability and reduced transferrin binding create favorable conditions for fungal

proliferation[18]. Before amphotericin B and surgical interventions, mortality exceeded 90% [19].

Patients with neutropenia or defective phagocytosis are at greater risk, although this is less evident in AIDS patients, suggesting T lymphocytes play little role in halting fungal proliferation compared to neutrophils [20]. Prolonged voriconazole therapy, particularly in patients with hematologic malignancies or transplants, also increases risk [21–25]. Cases have also been reported in individuals without identifiable immune deficiencies, often linked to burns, trauma, or iatrogenic factors [26–28].

Oral Manifestation with Rhino Cerebral Mucormycosis (ROCM)

Mucormycosis can present in two broad categories: Superficial vs. Visceral: Superficial: external ear, skin, nails; Visceral: pulmonary, gastrointestinal, rhino cerebral. Localized vs. Disseminated: Spores enter through the skin or respiratory tract—for instance, via contaminated food or needles [29,30]

ROCM is the most frequent form in diabetic patients but also occurs in individuals with malignancies, transplant recipients, and other immunocompromised hosts. The infection begins when spores reach the paranasal sinuses, then spread rapidly into surrounding tissues. The fungus can invade the palate, sphenoid sinus, cavernous sinus, or even the brain via the orbital apex or ethmoid bone. Vascular invasion may result in hematogenous dissemination or mycotic aneurysm formation [31].

Clinical Features

Initial symptoms resemble sinusitis or periorbital cellulitis, including: facial pain or numbness, periorbital swelling, blurred vision. Progressive features include: cranial nerve palsies, orbital inflammation, edema, proptosis, blepharoptosis, ophthalmoplegia (internal/external), severe headache, acute vision loss

A hallmark sign is the presence of a black necrotic eschar, though its absence does not rule out the disease. fever may be absent in half of patients. leukocytosis is typical if bone marrow function remains intact [32].

Role of Mucormycosis in Covid-19

COVID-19 presents with fever, hypoxia, altered osmolarity, and breathlessness[33]. Many recovered COVID-19 patients subsequently developed mucormycosis, with the fungus spreading to the sinuses, lungs, orbit, and even intracranial structures [33].

The immunosuppressive environment created by COVID-19, along with widespread corticosteroid use, significantly increases risk. Patients most vulnerable include diabetics, neutropenic individuals, transplant recipients, and those with hematologic malignancies [34].

Studies indicate diabetic patients are especially prone to COVID-19–associated mucormycosis [37,35]. Mechanisms linking diabetes with severe COVID-19 include: Impaired viral clearance, T-cell dysfunction, Cytokine storm exaggeration, Immunosuppression [33].

Hyperglycemia worsens cytokine storms by damaging endothelial cells and causing multi-organ injury. In diabetic ketoacidosis, acidic pH and excess free ferric ions further facilitate Mucorales growth and invasion [33].

Steroid therapy, while beneficial against COVID-19–induced inflammation, reduces white blood cell and T-helper cell activity, weakens immunity, and increases blood sugar levels, thereby creating a favourable environment for fungal invasion. Prolonged oxygen therapy and use of humidifiers/ventilators may add to the risk [36].

Although only limited case reports exist, the available evidence strongly supports these mechanisms as key contributors to the surge in mucormycosis among COVID-19 patients [36].

Challenges in Managing Mucormycosis

Mucormycosis carries a mortality rate of nearly 50%. COVID-19 patients, particularly those requiring oxygen therapy, face an elevated risk. Inhalation of spores in immunocompromised hosts leads to colonization, vascular invasion, and widespread tissue damage.

Uncontrolled diabetes remains the single most important risk factor due to high blood glucose levels and compromised immunity. Additional environmental factors such as warm, humid conditions and contaminated oxygen devices further promote infection. Delayed diagnosis and treatment dramatically worsen outcomes [37].

Radiographic Features

Sinus opacification is often accompanied by patchy erosion of the bony sinus walls. In cases of cavernous sinus thrombophlebitis, mucormycosis may present with the "black turbinate sign," which refers to a non-enhancing area of mucosa on MRI [38]. CT or MRI imaging may reveal thickened mucosa, opacified sinuses, congested extraocular muscles, orbital apex crowding, proptosis, and optic nerve inflammation [39]. In pulmonary mucormycosis, micro-nodules and multiple additional nodules may be detected, consistent with findings reported by Chamilos et al [40,41].

Histopathological Features

Histological examination of infected tissue typically reveals extensive necrosis with numerous broad, ribbon-like, pale-staining, non-septate hyphae branching at right or obtuse angles. Round or ovoid sporangia are commonly observed in cultures. The hyphae are thin-walled, usually non-septate, with irregular branching and occasional bulbous swelling, measuring 3–25 μm in diameter. Necrotic tissue with hyphae often demonstrates angio-invasion and infarction. In non-granulocytopenic patients, neutrophilic infiltration is seen, and chronic cases may show granuloma formation. Gomori Methenamine Silver (Grocott) and Periodic Acid-Schiff (PAS) stains are preferred for identification [42].

Diagnostic Methods

Diagnosis requires careful clinical assessment, supported by MRI and early CT imaging, as well as cytological and histological evaluations. Microbiological methods, molecular detection,[43] and host factor identification play a critical role in assessing the risk of invasive mucormycosis. Laboratory techniques include PAS staining, direct microscopy, calcofluor staining, histopathology, Gomori methenamine silver stain, culture, molecular assays, and fluorescent in situ hybridization. According to Kontoyiannis et al., challenges in diagnosis arise due to the nonspecific clinical presentation and occult dissemination of the disease. Tissue-based analysis remains the gold standard for confirmation [22].

Differential Diagnosis

Mucormycosis should be distinguished from maxillary sinus neoplasms, aspergillosis, soft tissue infarction, radionecrosis, and other deep fungal infections [44].

Treatment

Effective management involves prompt diagnosis, surgical debridement, antifungal therapy, and adjunctive options such as hyperbaric oxygen, recombinant cytokines, granulocyte transfusion, and prosthetic obturators. Spellberg et al. noted that monotherapy carries high mortality rates, particularly in haematology patients, and recommend combination therapy for improved outcomes [45].

Common antifungal regimens include Amphotericin B deoxycholate, liposomal Amphotericin B (5–10 mg/kg), Amphotericin B lipid complex, Amphotericin B colloidal dispersion, and Posaconazole (400 mg twice daily), along with management of underlying conditions. Second-line

therapy may involve combinations such as caspofungin with lipid Amphotericin B or lipid Amphotericin B with Posaconazole. Deferasirox is not recommended. Surgical intervention should be considered for soft tissue, cerebral, localized pulmonary, and rhino-orbito forms of mucormycosis [46].

Prognosis and Morbidity

Prognosis depends on disease extent and timely initiation of treatment. In rhino-cerebral mucormycosis, survival is about 75% in patients without systemic disease but drops to ~20% in those with comorbidities. Pulmonary mucormycosis is often fatal [47].

Survival rates vary by site: Rhino-cerebral: 45%, Focal cerebral: 33%, Pulmonary: 36%, Sinusitis (without cerebral involvement): 87%, Cutaneous isolated: 90%, Disseminated: 16%, Gastrointestinal: 10%. Better outcomes are associated with low baseline serum iron/ferritin levels, absence of neutropenia, and malignancies not complicated by infection [48].

Conclusion

COVID-19 has created global health challenges, and its treatment and complications have predisposed patients to secondary fungal infections like mucormycosis. This angioinvasive fungus, commonly found in soil, plants, dung, and decaying produce, becomes life-threatening when inhaled by immunocompromised hosts, particularly those with diabetes and those receiving corticosteroid therapy.

Once inhaled, fungal spores invade blood vessels, causing thrombosis, tissue necrosis, and infarction. High-risk groups include individuals with diabetic ketoacidosis, neutropenia, excess iron levels, and steroid-induced hyperglycaemia, all of which reduce WBC and T-cell activity and worsen cytokine storms.

To combat this fatal infection, timely diagnosis, antifungal therapy, surgical management when required, and a multidisciplinary treatment approach are essential. Future research must focus on clarifying the mechanisms of mucormycosis in COVID-19 patients and developing effective strategies for prevention and treatment. Diagnostic vigilance is crucial, particularly in COVID-19–positive and immunosuppressed individuals.

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