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Review Article

Evolution of mucormycosis – Systematic review and meta-analysis

Karthikeyan Padmanabhan[1]*, Kirubhagaran Ravichandran[1], Subhathra Radhakrishnan[1]

[1]*Dept. of Otorhinolaryngology and Head and Neck Surgery, Mahatma Gandhi Medical College and Research Institute, (A constituent college of Sri Balaji Vidyapeeth) SBV Campus, Pillayarkuppam, Pondicherry, India*

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ABSTRACT

The outbreak of COVID-19, caused by the novel coronavirus SARS-CoV-2, has been linked to a notable rise in mucormycosis cases, particularly evident during the second wave in the summer of 2021. Mucormycosis, characterized by its aggressive nature and high mortality rates, requires rapid identification and intervention. Factors such as poorly controlled blood sugar levels, corticosteroid usage, and COVID-19-related immune compromise are significant contributors to its development. The objective of this review is to analyze the incidence, progression, clinical manifestations, and treatment approaches of mucormycosis, drawing from a selection of 16 pertinent articles published between 2009 and 2022, and accessed through databases like PubMed and Google Scholar.

1. Introduction

The coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, has led to an increase in secondary fungal and bacterial infections, among which mucormycosis has emerged as a significant concern, particularly in regions such as India.[1] Mucormycosis, characterized by invasive fungal infection primarily affecting the sinuses and potentially spreading to the brain (cerebral mucormycosis),[2] poses a considerable threat, especially among individuals with uncontrolled diabetes and other immunocompromised states. Sinuses were the most common site of mucormycosis among COVID-19 patients at 79.4% with the maxillary sinus being the most commonly infected.[3] Rhino-orbit-cerebral is associated with uncontrolled diabetes is the predominant characteristic. Orbits were the second most prevalent site followed by lungs.[4] Although traditionally considered an opportunistic infection, mucormycosis can also affect immunocompetent individuals through various transmission routes, including inhalation of sporangiospores[5] and direct contact with contaminated sources. The preferred treatment approach involves surgical debridement followed by antifungal therapy, commonly employing lipid formulations of amphotericin B, to improve patient outcomes. Collaborative efforts among healthcare professionals are essential for early detection, management, and prevention of mucormycosis, especially in the ongoing pandemic.

2. Overview

Mucormycosis, characterized by its opportunistic and highly invasive nature, poses significant morbidity and mortality risks. Typically, onset occurs approximately two weeks post-COVID-19 diagnosis, predominantly affecting individuals with either recently diagnosed or poorly managed diabetes mellitus. Timely diagnosis and appropriate management greatly influence patient

* *Corresponding author*.
E-mail address: karthikent73@gmail.com (K. Padmanabhan).

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outcomes and survival rates. Despite aggressive medical interventions, including high-dose AmBisome therapy, and extensive surgical procedures, individuals with suboptimal blood sugar control continue to face elevated mortality rates and unfavorable prognoses. Treatment primarily involves lipid formulations of amphotericin B, supported by intensive surgical interventions. Various guidelines, such as the ECMM/MSG-ERC for salvage therapy in refractory cases, and those proposed by the All India Ophthalmological Society for mucormycosis diagnosis, offer essential frameworks for management.

2.1. Study selection

This article conducted an extensive review of the literature concerning the association between COVID-19 and mucormycosis. Using databases such as PubMed and Google Scholar, English-language research articles were identified using specific search terms like COVID-19/Pandemic, SARS-CoV-2, Mucormycosis, the second wave of coronavirus disease/mucormycosis, and coronavirus. To ensure reliability, two different individuals independently conducted the search process, with non-English articles and those unrelated to COVID-19 being excluded. Additionally, information from reputable sources like the World Health Organization (WHO), Centers for Disease Control and Prevention (CDC), and other credible institutions was integrated. The findings were systematically organized and presented in this review to provide a comprehensive analysis of the topic.[6]

2.2. Epidemiology and incidence

The actual incidence and prevalence of mucormycosis might be considerably higher than reported due to challenges in sample collection from deep tissues and the limited sensitivity of diagnostic tests. The Leading International Fungal Education (LIFE) portal has estimated the global burden of serious fungal infections. Initially, they projected an annual prevalence of around 10,000 mucormycosis cases worldwide, excluding India. However, upon the inclusion of Indian data, this estimate surged to 910,000 cases globally. This underscores a significant shift in the epidemiology of mucormycosis in recent years, marked by the emergence of new risk factors and causative agents.[7]

2.3. *L*aboratory investigation of mucormycosis:[8]

Tissue necrosis due to angioinvasion is a classic hallmark of mucormycosis, although other fungi like Aspergillus, Lomentospora (Scedosporium), and Fusarium spp. can also induce tissue necrosis. In such scenarios, a collaborative approach involving clinicians, histopathologists, microbiologists, and radiologists is crucial.

Table 1:

Disease manifestations	No. of patients N (%)	No. of proven cases n(%)	Overall mortality N(%)
Rhino-orbital-cerebral mucormycosis	288	254	120 (42%)
Localized sinus	158	136	53
Localized orbital	6	6	2
Localized cerebral	16	16	11
Sino-orbital	82	75	35
Sino-cerebral	20	16	15
Generalized rhino-orbital cerebral	6	5	4
Pulmonary mucormycosis	172	132	87
Localized	168	128	84
Deep extension	4	4	3
Cutaneous mucormycosis	187	172	58
Localized	150	137	46
Deep extension	37	35	12
Disseminated mucormycosis	110	101	75
Gastrointestinal mucormycosis	72	71	39
Others	22	20	10

Table 2: Risk factors

Diabetes mellitus
Autoimmune disorder
Iron overload
Burns
Trauma including surgery
Immuno suppressive therapy
Human immunodeficiency virus
Malnutrition

2.4. Endoscopic and radiological findings

Endoscopic and radiological assessments are pivotal in mucormycosis diagnosis. Endoscopy facilitates examination of the nasal cavity, particularly focusing on the middle turbinate and sinuses, providing initial indications of mucormycosis. Nasal computed tomography (NCCT) and magnetic resonance imaging (MRI) of the paranasal sinuses and orbit aid in diagnosis by revealing hyperinflated, dense sinus mucosa with bone erosion, including periosteal involvement. In cases of respiratory mucormycosis, high-resolution CT (HRCT) of the thorax may display characteristic findings such as the reverse

halo sign (RHS), multiple nodules (≥10), pleural effusion, central necrosis, and air crescent sign.

2.5. Microscopic findings

Microscopic examination is pivotal for diagnosis, necessitating caution to prevent interference from cotton fibers when collecting nasal secretions/discharge. Specimens should not be refrigerated, as Mucorales do not thrive under low temperatures. Direct microscopic examination and cultivation are conducted using the black-colored area of excised tissue. Various diagnostic techniques include potassium hydroxide (KOH) wet mount, Calcofluor white (CFW) stain, culture, and molecular methods.

2.6. Histological findings

Histological analysis involves sending excised tissue in a sterile container with 10% formalin to maintain tissue integrity. The initial gross examination is followed by tissue sectioning and paraffin embedding through dehydration, clearing, and infiltration. The embedded paraffin block is then sliced into multiple 4-5-micrometer thick sections, stained with Hematoxylin and Eosin (H&E) for microscopic evaluation.

3. Management

3.1. Conservative management

3.1.1. Amphotericin B (ABCL, AMB, LAMB)

All patients were initiated on intravenous amphotericin B in addition to oral administration of a saturated solution of potassium iodide in drop form. Among them, twenty-four patients received liposomal amphotericin B, while one patient was treated with conventional amphotericin B deoxycholate. Newer lipid formulations, including liposomal amphotericin B, amphotericin B lipid complex, and amphotericin B cholesteryl sulfate complex, are considered less toxic compared to traditional varieties. While amphotericin B has been traditionally considered the first-line treatment for invasive candidiasis, mucormycosis, and aspergillosis, its popularity is declining with the advent of new azole-derived antifungals due to their broader spectrum of activity and improved safety profile.[9] Fungicidal activity is dose-dependent and typically lasts up to 12 hours. The recommended dose ranges from 0.7 to 1 mg/kg/day, administered slowly over 2 to 4 hours to reduce the risk of cardiotoxicity. The dosage for central nervous system (CNS) involvement is 1 mg/100g per day for liposomal amphotericin B, while for cases without CNS involvement, it is 0.5 mg/100g per day, with a treatment duration of 6 to 12 weeks.

3.1.2. Posaconazole

Posaconazole, administered orally at a dosage of 400 mg twice daily, results in serum levels below 1 μg/mL with considerable variability. Previously, posaconazole was administered intravenously or orally at a dosage of 1 x 300 mg from day 2, followed by 2 x 300 mg on day 1, for 6 months. Alternatively, oral suspension could be administered at a dosage of 2 x 400 mg/day or 4 x 200 mg/day.

3.1.3. Combined antifungal therapy

Combination antifungal therapy, such as liposomal amphotericin B combined with micafungin or anidulafungin, has shown improved outcomes in cases of disseminated mucormycosis, especially in neutropenic and diabetic ketoacidosis (DKA) patients.

3.1.4. Iron chelation therapy

Iron chelation therapy with deferoxamine predisposes individuals to mucormycosis. Deferasirox, an orally available iron chelator, has been used as the iron overload therapy for patients with transfusion-dependent anemia. Proinflammatory cytokines like interferon-γ and granulocyte-macrophage colony-stimulating factors enhance granulocyte function against mucormycosis agents.

3.1.5. Isavuconazole

Isavuconazole, a broad-spectrum triazole, is approved for mucormycosis treatment. The recommended dosage is 3 x 200 mg on day 1, followed by 1 x 200 mg from day 3, for 3 months, administered via intravenous or oral routes.

3.1.6. Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBO) has been proposed as an adjunct therapy to surgical and antifungal treatments for mucormycosis, particularly in immunocompromised patients with sinusitis or cutaneous mucormycosis. HBO increases oxygen pressure, enhances neutrophil function, promotes amphotericin B action by reversing acidosis, inhibits fungal growth, and improves wound healing. Immune-augmentation strategies, such as administration of granulocyte (macrophage) colony-stimulating factor or interferon, have been suggested based on limited in vitro data and case reports.[10]

4. Surgical Management

Sequenctial action of thrombosis and subsequent tissue necrosis during mucormycosis can impede the effective penetration of antifungal agents into the infected site. Therefore, the removal of dead tissues is deemed crucial for achieving complete eradication of prevailing disease. Analysis through logistic regression has independently identified surgery as a determining factor for favorable outcomes among patients with mucormycosis. Several case

series have consistently demonstrated significantly higher mortality rates in patients who did not undergo surgical debridement compared to those who did.

Although potential selection bias may exist in this case series due to differences in severity of the disease or comorbidities, the data strongly advocate for the necessity of surgical debridement in optimizing cure rates.

Nevertheless, the ideal extent and time for debridement for maximizing mucormycosis outcomes remain undefined.

Functional endoscopic sinus surgery (FESS) with debridement was performed in all patients. Additionally, total orbital exenteration was carried out in 6 patients (24%), while maxillectomy was undertaken in another 6 patients (24%). Six patients (24%) necessitated alveolectomy during the second week of treatment following initial stage debridement.[11]

Limited evidence from a retrospective review suggests an "aggressive conservative" approach. This strategy involves utilizing intraoperative frozen sections to delineate infected tissue margins and sparing uninvolved tissues from debridement whenever feasible.[12]

5. Recent Advances

Recent therapeutic advancements hold promise for improving mucormycosis outcomes. Lipid formulations of amphotericin B (LFAB) have emerged as the primary therapy and posaconazole may serve as salvage therapy. Pre clinical and limited retrospective clinical evidence suggests that combination LFAB-echinocandin therapy may enhance survival rates, but needs definitive trials for validation. Combining LFAB with the iron chelator has shown improved outcomes in animal models. Conversely, polyene-posaconazole combination therapy has shown no preclinical benefit. Selected patients may benefit from adjunctive therapy with recombinant cytokines, hyperbaric oxygen, or granulocyte transfusions. Early detection and initiation of treatment is crucial, and advancements in polymerase chain reaction technology offer promise for early diagnosis. Prospective, randomized clinical trials are essential to determine optimal management strategies for mucormycosis. There is an urgent need for improved diagnostic, treatment, and prevention tools, including new radiographic, molecular, and antigenic methods for early detection and monitoring. Exploration of newer drugs and combinations, both in laboratory and clinical settings, is crucial. Designing informative clinical trials for this life-threatening infection poses challenges but requires innovative approaches. Definitive clinical data are essential for refining therapeutic recommendations. Understanding the fundamental molecular, metabolic, and immunological characteristics of these organisms is paramount for advancing our knowledge of mucormycosis.[12–16]

6. Source of Funding

None.

7. Conflict of Interest

None.

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Author biography

Karthikeyan Padmanabhan, Professor & HOD https://orcid.org/0000-0002-1992-6802

Kirubhagaran Ravichandran, -

Subhathra Radhakrishnan, -

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