CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

Available online at: http://www.iajps.com *Review Article*

REVIEW ON MUCORMYCOSIS

Mrs. Savitha Mol G M[1*], Mrs. Aswathy S S[2], Mrs. Remya S B[3], Mrs. Aparna P[4], Dr. Silvia Navis A[5], Dr. Prasobh G R[6]

[1]Associate Professor, Department of Pharmacology, Sree Krishna College of Pharmacy & Reasearch Centre, Parassala, Thiruvananthapuram

[2]Assistant Professor, Department of Pharmacology, Sree Krishna College of Pharmacy & Reasearch Centre, Parassala, Thiruvananthapuram

[3]Associate Professor, Department of Pharmaceutics, Sree Krishna College of Pharmacy & Reasearch Centre, Parassala, Thiruvananthapuram

[4]Associate Professor, Department of Pharmaceutics, Sree Krishna College of Pharmacy & Reasearch Centre, Parassala, Thiruvananthapuram

[5] Head of Pharmacology Department, Sree Krishna College of Pharmacy & Reasearch Centre, Parassala, Thiruvananthapuram

[6] Principal, Sree Krishna College of Pharmacy & Reasearch Centre, Parassala, Thiruvananthapuram

Article Received: November 2021 **Accepted:** November 2021 **Published:** December 2021

Abstract:

Mucormycosis is the third invasive mycosis in order of importance after candidiasis and aspergillosis and is caused by fungi of the class Zygomycetes. The most important species in order of frequency is Rhizopus arrhizus (oryzae). Identification of the agents responsible for mucormycosis is based on macroscopic and microscopic morphological criteria, carbohydrate assimilation and the maximum temperature compatible with its growth. The incidence of mucormycosis is approximately 1.7 cases per1000000 inhabitants per year, and the main risk-factors for the development of mucormycosis are ketoacidosis (diabetic or other), iatrogenic immunosuppression, use of corticosteroids or deferoxamine, disruption of mucocutaneous barriers by catheters and other devices, and exposure to bandages contaminated by these fungi.

The standard guidelines in management of mucormycosis involves early diagnosis, a reversing risk factors and underlying illness, surgical debridement, and immediate intravenous antifungals - usually amphotericin B. This include the prompt management of hyperglycaemia, acidosis, electrolyte imbalance and cessation of immunosuppressive drugs.

Corresponding author:

Savitha Mol G M,

Department of Pathology, King Hamad University Hospital, Bahrain.

QR code

Please cite this article in press ***Savitha Mol G M*** *et al,* **Review On Mucormycosis,** *Indo Am. J. P. Sci, 2021; 08(12).*

INTRODUCTION:

Mucormycosis is an infection caused by fungi that belong to the Mucorales order. Mucormycosis is a type of invasive fungal infection caused by mold fungi. Mucoralean fungi can reproduce both sexually and asexually. The asexual sporangio spores reformed in a globe-like structure called the sporangium on the apex of sporangiophore. The sporangiospores then disperse and, on appropriate conditions, germinate to produce a mycelial complex. Most of the pathogenic Mucorales are heterothallic, and in their sexual development, hyphae of the two different mating types sensitize each other and undergo fusion to form zygospores, which later germinate to form a sporangium at the apex culminating in sexual meiospores. The formation of zygospores requires two compatible mating types, and it takes a considerable amount of time for the zygospores to germinate. Therefore, the asexual sporangiospores may serve as the main source of dissemination and infection. Infection sites include the lungs, rhinocerebral spaces, sinuses, soft tissue, skin, gastrointestinal tract, and bloodstream[1].

In 60% of mucormycosis cases in humans, Rhizopus *oryzae* is the commonest aetiology which is responsible for 90% of the rhino cerebral form whereas pulmonary mucormycosis is a relatively rare fungal disease, which is arduous to diagnose early and lacks effective treatment. The rise in cases of mucormycosis is due to COVID – 19, which remain correlated with the impaired immune system of infected patient[2]. SARS-CoV-2 infection manipulates the immune system by affecting T lymphocytes, especially CD4+ and CD8+ T cells, which is highly involved in the pathological process of COVID -19 infection. Significant reduction in the absolute number of lymphocytes (lymphopenia) and specifically of T cells involved in the most severe COVID -19 cases, is associated with the worst outcome compromising the immune system and might expose patients to a higher risk of developing opportunistic infections[3].

EPIDEMIOLOGY

Approximately 1.7 cases per 1000 000 inhabitants per year,is the incidence of mucormycosis in which, 500 patients per year in the USA. Postmortem evaluation of the presence of agents responsible for mucormycosis shows that mucormycosis is ten- to 50-fold less frequent than candidiasis or aspergillosis, and that it appears in one to five cases per 10 000 autopsies[4].

The main risk-factors for the development of mucormycosis are ketoacidosis (diabetic or other), iatrogenic immunosuppression, especially when it is associated with neutropenia and graft vs. host disease in haematological patients, use of corticosteroids or deferoxamine, disruption of mucocutaneous barriers by catheters and other devices, and even exposure to bandages contaminated by these fungi[5].

PATHOGENESIS

Mucorales mainly invade deep tissues via inhalation of airborne spores, percutaneous inoculation or ingestion. They colonise a high number of patients but do not necessarily cause invasion. Once the spores have penetrated the lungs or subcutaneous tissues, they are met by the first line of defence, mononuclear and polynuclear phagocytes. The phagocytes of the healthy host are able to killor destroy the spores of Mucorales by generating oxidative metabolites and defensing(cationic peptides). Severely immuno compromised neutropenic patients and those with phagocyte dysfunction (e.g., hyperglycaemia) are at greater risk of mucormycosis. Ketoacidosis decreases the movement of these phagocytes towards the source of the infection and their capacity for lysis by oxidative and non-oxidative mechanisms[6,7].

Lymphopenia is common in patients infected with SARS-COV2 and may rise preponderance to mucor infection with further suppression of the immune system. This susceptibility has been documented especially by mucor infections observed in AIDS patients with lymphopenia suggesting that lymphopenia associated with COVID -19 may also be a primary risk factor for mucor infection. The spores of the inhaled fungus are destroyed by the phagocytic cells, but in immunocompromised individuals, the vascular endothelium is infected by the spores through invasion[8].

As in fungal infection, host response involves both cellular and humoral immunity where, the latter plays a major role in offering defence against fungal infection. It has been also reported that cellular immunity associated with Th1-type offer a protective response against fungal infection via secreting IFN-y[9]. The central research institution across the globe such as CDC emphasizes rise in mucormycosis cases after COVID-19 disease[10].

RESPIRATORY MANIFESTATIONS

Invasion of the lung is the second most common clinical manifestation and follows the inhalation of spores. The most frequent predisposing underlying condition has been considered to be haematological malignancy with neutropenia, although recent studies

suggest that diabetes mellitus is the most frequent underlying condition[11].

The radiological presentation of mucormycosis is similar to that of invasive aspergillosis, and both tend to show vascular invasion and thrombosis, followed by tissue necrosis.presentation includes cuneiform pulmonary infiltrates, pulmonary nodules and cavitated lesions, including the 'halo' sign. Currently, one of the most controversial issues is the spectacular increase in the number of cases of mucormycosis in institutions that care for haemato-oncological patients. This increase has generally taken place in patients and units where broad-spectrum antifungal prophylaxis, especially voriconazole, is used against Aspergillus[12].

The poor and or impaired immune functioning is major cause of rise in mucormycosis cases and clinical findings further confirmed in COVID – 19 patients. The cell mediated immunity i.e. Th1 and IFN-y are primarily involved in providing protection during viral infections.

However, novel SARS-CoV-2 infection remains associated with impaired functioning of not only cellular but also humoral immunity triggering higher risk for fungal infection[13].

In short, the multiple risk factors present in the patients or the co-morbid illnesses in severe COVID-19 patients, along with the additional immunosuppression caused by glucocorticoids, increases the net effect of an immune suppression, thereby making liable to invasive mold infections[14].

Diagnosis

Rapid diagnosis and initiation of therapy is critical due to the acute, fulminate nature of the infection.Diagnosis of mucormycosis rests upon the presence of predisposing conditions, signs and symptoms of disease, observation of fungal elements of specific morphology in histological sections, and direct smears of material, and, to a lesser extent, culture re-sults.There are no reliable serological methods for diagnosis at present[15].

Direct examination in 10% KOH of scrapings from the upper turbinates, aspirated sinus material, sputum, and biopsy material can be valuable. The presence of thick-walled, aseptate, and refractile hyphae 6 to 15 µm in diameter, with some hyphae being swollen and distorted, is indicative of the presence of Mucorales fungi.Histological sections show acute suppurative inflammation with focal areas of granulomatous inflammation[16]. There are aseptate hyphae 6 to 50 µm in diameter, branching at 90°. The hyphae invade the adjacent blood vessel walls, producing thrombosis and infarction, but rarely disseminate through the vessels. Staining with Grocott-Gomori methenamine silver is best, though periodic acid-Schiff and hematoxylin & eosin (H&E) stains can be used[17].

Treatment

Once diagnosis has been established, correction of hypoxia, acidosis, hyperglycemia, and electrolytic imbalance needs to be undertaken. Steroids, anti-metabolites, and immunosuppressive drugs should be discontinued, if possible. Aggressive surgical debridement is usually undertaken, along with high dose intravenous amphotericin B therapy (5mg/kg IV daily)[18]. Treatment is continued until remission is achieved. Liposomal amphotericin B may be more effective and less toxic. Resistance to amphotericin B has been observed with prolonged therapy. Local irrigation and packing to aid delivery of amphotericin B to necrotic and poorly perfused tissues has been tried as an adjunct to therapy. This could help prevent disfiguring surgery[19].

Steroidal therapy to the patient can be another underlying cause for the development of mucor infection[20].

Local irrigation and packing to aid delivery of amphotericin B to necrotic and poorly perfused tissues has been tried as an adjunct to therapy. This could help prevent disfiguring surgery[21].

The recent discovery for the management of mucormycosis advocate Liposomal Amphotericin B at a dose of 5–10 mg/kg per day in high doses intravenously as initial therapy and without central nervous system involvement, a dose of 5 mg/kg is recommended.

It is understood that from a randomised controlled trial of 201 patients with invasive mold disease administrated liposomal amphotericin B used at 3 mg/kg/day showed equal efficacy but safer and better tolerated 10 mg/kg/day dose amphotericin B[22].
The initial starting dose is 5 mg/kg IV daily, with a maximum dose of 10 mg/kg IV and the duration of treatment depends upon the patient's clinical picture.
Surgical debridement of infected tissue is mandatory to limit the further spread of infection. Aggressive surgical debridement of necrotic tissue should be promptly done which may involve lobectomy, partial pneumonectomy in accordance with the site of disease. Similar to necrotizing fasciitis, this advocates

aggressive surgical management and often carried dramatic morbidity[23]. Without restoring immune status, the outcomes are unfortunately very bad even with the standard antifungal therapies and surgical debridement.

Posaconazole or Isavuconazole has some evidence as second-line therapy in mucormycosis. As for rescue management, Posaconazole 200 mg IV four times daily is recommended. Amphotericin and Posaconazole combination are not supported by guidelines. Hyperbaric oxygen is used as an adjuvant therapy. The elevated oxygen pressure improves the ability of neutrophils to kill the fungi and enhances wound healing.

Management of rhino-orbital cerebral mucormycosis also involves medical as well as surgical management which is regarded as an emergency[24].

A three-step approach of reversal of immunosuppressive state, administration of IV antifungals, and extensive surgical debridement is usually undertaken.
Early definite diagnosis is practically challenging, whereas the delay in initiating the treatment will further exasperate the morbidity and mortality. Prompt antifungal administration and extensive surgical debridement are carried out empirically whenever the possibility of rhino-orbital cerebral mucormycosis is suspected based on risk factors, clinical features, and or radiologic findings. Granulocyte colony-stimulating factor may enhance white blood cell count and may help to improve host defences.

For definite histopathologic confirmation, debridement provides adequate tissue biopsy. Dissection is usually continued until normal, well-perfused bleeding tissue is attained, since mucormycotic tissues are less likely to bleed due to extensive thrombosis of vessels. Removal of the palate, nose cartilage, and orbit would cause significant disfigurement. The orbital involvement may need orbital decompression or exenteration. The relevance of routine orbital exenteration or the timing exenteration is currently unclear, and cases with orbital involvement have also been successfully managed without exenteration[25].

CONCLUSION:

The rise in cases of mucormycosis is due to COVID – 19, which remain correlated with the impaired immune system of infected patient. Diabetes is one of the major risk factors because the growth of fungi is stimulated by a high blood glucose concentration, infection is rare in patients with well-controlled blood glucose levels. If infection is confirmed, early surgical intervention and intravenous anti-fungal treatment should be advocated for management, as a better prognosis and less fulminate disease course can be achieved in cases of post-coronavirus mucormycosis. This also include the prompt management of hyperglycaemia, acidosis, electrolyte imbalance and cessation of immunosuppressive drugs. Identifying the risk factors and the comorbidities is mandatory to reverse the condition and reduce the mortality in patients.

REFERENCES:

1. Prabhu RM, Patel R. Mucormycosis and entomophthoramycosis: a review of the clinical manifestations, diagnosis and treatment. Clin Microbiol Infect, 2004; 10(1): 31–47.
2. Randhawa HS, Budimulja U, Bazaz-Malik G, Bramono K, Hiruma M, Kullavanijaya P, Rojanavanich V. 1994. Recent developments in the diagnosis and treatment of subcutaneous mycoses. Med Mycol 32: 299–307.
3. Waldorf AR. Pulmonary defense mechanisms against opportunistic fungal pathogens. Immunol Ser., 1989; 47: 243–271.
4. Waldorf AR, Ruderman N, Diamond RD. Specific susceptibility to mucormycosis in murine diabetes and bronchoalveolar macrophage defense against Rhizopus. J Clin Invest, 1984; 74: 150–160.
5. Song WK, Park HJ, Cinn YW, Rheem I, Pai H, Shin JH. Primary cutaneous mucormycosis in a trauma patient. J Dermatol 1999; 26: 825–828.
6. Hotchi M, Okada M, Nasu T. Present state of fungal infections in autopsy cases in Japan. Am J Clin Pathol 1980; 74: 410–416.
7. Tietz HJ, Brehmer D, Janisch W, Martin H. Incidence of endomycoses in the autopsy material of the Berlin Charite Hospital. Mycoses 1998; 41 (suppl 2): 81–85.
8. Yamazaki T, Kume H, Murase S, Yamashita E, Arisawa M. Epidemiology of visceral mycoses: analysis of data in annual of the pathological autopsy cases in Japan. J Clin Microbiol 1999; 37: 1732–1738.
9. Waldorf AR. Pulmonary defense mechanisms against opportunistic fungal pathogens. Immunol Ser 1989; 47: 243–271. 33. Waldorf AR, Ruderman N, Diamond RD. Specific susceptibility to mucormycosis in murine diabetes and bronchoalveolar macrophage defense against Rhizopus. J Clin Invest 1984; 74: 150–160.
10. Diamond RD, Haudenschild CC, Erickson NF 3rd. Monocyte-mediated damage to Rhizopus

oryzae hyphae in vitro. Infect Immun 1982; 38: 292–297.
11. Chinn RY, Diamond RD. Generation of chemotactic factors by Rhizopus oryzae in the presence and absence of serum: relationship to hyphal damage mediated by human neutrophils and effects of hyperglycemia and ketoacidosis. Infect Immun 1982; 38: 1123–1129.
12. Spellberg B, Edwards J Jr, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. Clin Microbiol Rev 2005; 18: 556–569.
13. . Lehrer RI, Howard DH. Mucormycosis. Ann Intern Med 1980; 93: 93–108.
14. Bigby TD, Serota ML, Tierney LM Jr, Matthay MA. Clinical spectrum of pulmonary mucormycosis. Chest 1986; 89: 435–439.
15. Lee FY, Mossad SB, Adal KA. Pulmonary mucormycosis: the last 30 years. Arch Intern Med 1999; 159: 1301–1309.
16. Dobrilovic N, Wait MA. Pulmonary mucormycosis. Ann Thorac Surg 2005; 79: 354.
17. Funada H, Matsuda T. Pulmonary mucormycosis in a hematology ward. Intern Med 1996; 35: 540–544.
18. Diamond RD, Haudenschild CC, Erickson NF 3rd. Monocyte-mediated damage to Rhizopus oryzae hyphae in vitro. Infect Immun, 1982; 38: 292–297.
19. Boelaert JR, de Locht M, Van Cutsem J et al. Mucormycosis during deferoxamine therapy is a siderophoremediated infection. In vitro and in vivo animal studies. J Clin Invest, 1993; 91: 1979–1986.
20. Nosari A, Oreste P, Montillo M et al. Mucormycosis in hematologic malignancies: an emerging fungal infection. Haematologica 2000; 85: 1068–1071.
21. Jimenez C, Lumbreras C, Aguado JM et al. Successful treatment of mucor infection after liver or pancreas–kidney transplantation. Transplantation 2002; 73: 476–480.
22. Nampoory MR, Khan ZU, Johny KV et al. Invasive fungal infections in renal transplant recipients. J Infect 1996; 33: 95–101.
23. Morduchowicz G, Shmueli D, Shapira Z et al. Rhinocerebral mucormycosis in renal transplant recipients: report of three cases and review of the literature. Rev Infect Dis 1986; 8: 441–446.
24. Sehgal A, Raghavendran M, Kumar D, Srivastava A, Dubey D, Kumar A. Rhinocerebral mucormycosis causing basilar artery aneurysm with concomitant fungal colonic perforation in renal allograft recipient: a case report. Transplantation 2004; 78: 949–950.
25. Quinio D, Karam A, Leroy JP et al. Zygomycosis caused by Cunninghamella bertholletiae in a kidney transplant recipient. Med Mycol 2004; 42: 177–180.