ejpmr, 2021,8(8), 730-734

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

MUCORMYCOSIS- EPIDEMIOLOGY (FUNGAL INFECTION) ACCOMPYING WITH THEIR TYPES

Akshada Ashok Shinde*

Student, Marathwada Mitra Mandal College of Pharmacy, Thergaon (kalewadi) Pune 411033.

***Corresponding Author: Akshada Ashok Shinde**

Student, Marathwada Mitra Mandal College of Pharmacy, Thergaon (Kalewadi) Pune 411033.

Article Received on 20/06/2021 **Article Revised on 11/07/2021** **Article Accepted on 01/08/2021**

ABSTRACT

Mucormycosis is earlier known as zygomycosis. This is a serious but infrequent fungal infection caused by a group of molds called mucormycetes. These molds live amongst all the environment. It usually occurs in immune compromised individuals like diabetic ketoacidosis, leukemia, lymphoma, severe malnutrition, high dose corticosteroids and organ transplantation. It can be categorized into rhino-orbitocerebral, cutaneous, disseminated, gastrointestinal, and pulmonary types. New strategies to prevent and treat mucormycosis are urgently needed. In this article we summarize etiopathogenesis of mucormycosis, types, symptoms, treatmentarrangement. Fungal infections, mucormycosis have been reported in patients with severe COVID-19.

KEYWORDS: Mucormycosis, Zygomycosis, Ketoacidosis, Rhino-orbitocerebral, Fungal infection.

INTRODUCTION

The disease was first described in 1876 when Fürbinger described in Germany a patient who died of cancer and in whom the right lung showed a hemorrhagic infarct with fungal hyphae and a few sporangia. In 1885, Arnold Paltauf published the first case of disseminated mucormycosis, which he named "Mycosis mucorina".[1] Mucormycosis is an infectious disease caused by fungi belonging to the order Mucorales (subphylum Mucormycotina).[2] Compared to other fungal pathogens, such as Aspergillusfumigatus or Candida albicans, only little is known so far on fungal properties leading to successful infection and host immune response to the various representatives of the Mucorales.[3]

The major risk factors for mucormycosis include uncontrolled diabetes mellitus in ketoacidosis, other forms of metabolic acidosis, treatment with corticosteroids, organ or bone marrow transplantation, neutropenia, trauma and burns, malignant hematologic disorders, and deferoxamine therapy in patients receiving hemodialysis.[4] Inhalation of sporangiospores is the most common route of transmission, although ingestion of spores, direct implantation into injured skin (burns), trauma with contaminated soil, or intravenous (drug users) transmission. After nasal inoculation it takes a rapidly progressive course extending to neighboring tissues, including the orbit, and sometimes to the brain.[5]

The mortality of mucormycosis remains high. Treatment includes antifungal agents in combination with surgical intervention[6] Clearly new strategies to prevent and treat mucormycosis are urgently needed, and such strategies can be facilitated by clear understanding of the pathogenesis of the disease.[4]

Types

- RhinocerebralMucormycosis (sinus and brain)
- Pulmonary Mucormycosis (lung)
- Gastrointestinal Mucormycosis
- Cutaneous Mucomycosis (skin)
- Disseminated Mucormycosis

Rhinocerebral Mucormycosis (sinus and brain)

Rhinocerebral mucormycosis is also called zygomycosis, is a rare disease caused by filamentous fungi concern the nose, paranasal sinuses, and brain. It is an opportunistic pathogen often found in immunocompromised individuals.[7] Mucorales is infects to the head and neck region in well-defined stages. Infection begins in the palate or the paranasal sinuses, progresses to the orbit, if not diagnosed early, to the brain.[8]

The most common symptoms include fever, obnubilation, amaurosis, proptosis, epistaxis, facial paralysis and sign of invasion of the trigeminal nerve. Thrombosis of the cavernous sinuses and cranial invasion may be consequences of unresolved rhino-sinus mucormycosis.[9]

Early on, paranasal sinus involvement may manifestas benign mucosal thickening on computed tomography. Bone destruction formation later. Mucorales occupy the retro-orbital region and frontal lobes by extending through the ethmoid or sphenoid sinuses. It can also be occupying the brain through the superior orbital fissure,

ophthalmic vessels, perineural route, cribiform plate or the carotid artery.[8]

The First-line medical therapy is amphotericin B (5 mg/kg/day) and may involve an additional IV antifungal agent such as the caspofungin for 6–8 weeks. Oral antifungals are often prescribed after the IV regimen is completed. Novel antifungals such as posaconazole and isavuconazole have shown promise as a salvage therapy. This is the especially important given the systemic adverse effects seen with amphotericin B.[10]

Pulmonary Mucormycosis (lung)

Pulmonary mucormycosis is an uncommon but life-threatening opportunistic fungal infection. It normally affects immunocompromised patients, such as recipients of stem cell or organ transplant, and has worse outcomes in those with hematologic malignancy or neutropenia.[11]

The first case of pulmonary mucormycosis was described in 1971 by Furbringer. In a classic review in 1971, Baker thoroughly describes all cases of mucormycosis previously reported.[12]

Pulmonary mucormycosis may develop as a result of inhalation of spores or by hematogenous or lymphatic spread. the entrance for Mucorales is the respiratory tract where the fungi can easily invade arteries, veins, and lymphatics and produce the thrombosis and infarction which can be fatal.[13] Mucorales fungi are ubiquitous saprophytic fungi that grow in decaying organic matter, particularly fruit with a high sugar content, soil and manure. Although the fungi are able to grow in anaerobic, aerobic and microaerophilic conditions, clinical specimen cultures often prove to be negative, making the diagnosis difficult. There has been previously no serological test for mucormycosis. The symptoms the pulmonary mucormycosis are generally non‑specific, even at late stages of infection, and may include fever, dyspnea, coughing and chest pain. Rare cases can present as progressive subcutaneous emphysema, Pancoast syndrome, Horner's syndrome, or chronic mediastinitis and bronchial perforation.[14] Pulmonary mucormycosis has a parallel radiographic appearance to aspergillosis. Both infections have a propensity to invade blood vessels and produce thrombosis.[8]

Successful treatment of the pulmonary mucormycosis relies on a timely diagnosis. Amphotericin B, along with a surgical resection of the involved areas of the lung and treatment of the underlying disease, is the mainstay of treatment. Despite the risk of renal toxicity, amphotericin B (1-1.5 mg/kg/day) remains the gold-standard antifungal agent used against mucormycosis.[14] Clinical experience with posaconazole, effective is in vitro and in vivo studies against mucor, is limited in pulmonary mucormycosis; it is still used as the second line therapy.[15]

Gastrointestinal Mucormycosis

Primary gastric mucormycosis is a rare but potentially lethal fungal infection due to the occupation of Mucorales into the gastric mucosa. It may result in the high mortality due to increased risk of the complications in immunocompromised patients.[16] The stomach is the most common site of gastrointestinal mucormycosis, followed by the colon and ileum. Gastrointestinal mucormycosis seen primarily in premature neonates, often in association with wide spread disseminated disease.[17]

The signs and symptoms of gastrointestinal mucormycosis are nonspecific, and include abdominal pain, hematemesis and melena. Patients who have undergone organ, bone marrow or peripheral blood stem cell transplantation, and those with acute myelogenous leukemia, lymphoma, diabetic ketoacidosis, nonketotic diabetes mellitus, amoebic colitis, typhoid fever, pellagra, kwashiorkor, malaria, malnutrition, meningococcemia and prematurity have developed gastrointestinal mucormycosis. Gastrointestinal mucormycosis has hardly ever occurred after renal, liver and heart transplantation.[8]

Medical management with antifungal therapy such as lipid formulation of amphotericin B, posaconazole, and currents agents isavuconazole or triazole is the mainstay option for the treating gastric mucormycosis.[16]

Cutaneous Mucormycosis (skin)

Cutaneous mucormycosis is a come out fungal infection caused by opportunistic fungi of the phylum Glomeromycota.[18]

Primary cutaneous mucormycosis resulting from direct immunization of fungi into the skin is rare and is generally seen in diabetics, in patients with thermal burns, and in immunocompromised patients. Secondary cutaneous mucormycosis is caused by hematogenous dissemination from an injury located elsewhere in the body in patients with primarily diabetes, hematologic malignancy, or immunodeficiency (e.g., AIDS patients and drug addicts).[19]

Cutaneous Mucormycosis involvement is less common than these, and it mainly occurs in two forms a “benign” well-localized subcutaneous form, which usually occurs due to the infection by the Entomophthorales, and a more explosive cutaneous infection with necrotizing fasciitis, systemic sepsis, and a fatal outcome if the diagnosis and consequently the appropriate treatment is delayed.[20] Cutaneous mucormycosis its look like blisters or ulcers, and the infected area is may turn black. Other symptoms are including pain, warmth, excessive redness, or swelling around the wound. Cutaneous mucormycosis can manifest as a superficial infection.[8]

The treatment for cutaneous zygomycosis is aggressive surgical debridement along with antifungal therapy.

Amphotericin B is the drug is select since these fungi are resistant to the majority of the antifungal drugs available. Posaconazole is also effective, but itraconazole and voriconazole have does not shown efficacy in these infections.[20]

Disseminated Mucormycosis

Disseminated mucormycosis is come out the infection spreads through the bloodstream to affect the another part of the body. The infection is most commonly affects to the brain, but also can affect other organs such as the spleen, heart, and skin.

Disseminated mucormycosis involves two or more noncontiguous organs. Neutropenic patients with leukemia or lymphoma comprise the majority of patients with disseminated mucormycosis. The risk factors for dissemination include organ transplantation, chemotherapy, corticosteroids and deferoxamine therapy.[8]

Excellent premorbid functional status and prompt recovery of the neutrophil count, a decision was made to treat this disseminated mucormycosis aggressively utilizing combination antifungal therapy and targeted surgical debridement of fungal foci.[25]

(COVID-19) Associated Mucormycosis

The pandemic corona virus disease 2019 (COVID-19) continues to be a serious significant problem worldwide.[21] The present second wave of the COVID-19 pandemic in India has we seen a rise in the rhino-orbital mucormycosis co-infections in COVID-19 patients.[22]

The most usual region affected is the nose, paranasal sinus, and brain leading to rhino-orbital and rhino-cerebral mucormycosis; this is also seen in the present pandemic and most of the case reports are of rhino-orbito-cerebral mucormycosis; although, there are also reports of pulmonary and gastrointestinal mucormycosis.[23]

The primary reason that appears to be facilitating Mucorales spores to germinate in people with COVID-19 is an ideal environment of low oxygen (hypoxia), high glucose (diabetes, new onset hyperglycemia, steroid-induced hyperglycemia), acidic medium (metabolic acidosis, diabetic ketoacidosis), high iron levels and decreased phagocytic activity of white blood cells (WBC) due to immunosuppression (SARS-CoV-2 mediated, steroid-mediated or background comorbidities) coupled with several other shared risk factors including prolonged hospitalization with or without mechanical ventilators.[26]

Present history of COVID- 19, the severity of COVID-19, the time from COVID- 19 to mucormycosis diagnosis, presence or absence of diabetic ketoacidosis, the clinical category of mucormycosis, the fungal species are isolated from clinical specimens, whether corticosteroids had been used for the management of COVID- 19, use of other treatment modalities (like remdesivir, tocili-zumab, convalescent plasma, antivirals and antibiotics), antifungal drug(s) used, any adjunct surgery performed for mucormycosis, investigations (blood glucose, C- reactive protein, ferritin, D- dimer and creatinine) and reported patient outcome.[24]

Many challenges have also emerged in the management of mucormycosis during this pandemic. Early detection, control of hyperglycemia, liposomal amphotericin B, and surgical debridement are the cornerstones in the successful management of mucormycosis.[23]

Treatment

Mucormycosis were difficult-to-manage infections owing to limited diagnostic tools and therapeutic options. advances in pathology understanding, diagnostic tools including computed tomography, and serum polymerase chain reaction and therapeutic options.[27]

The more current therapeutic developments in mucormycosis treatment are: the lipid formulations of amphotericin B, which are now the drugs of choice. Amphotericin B has shown admirable activity against the Mucorales in various in vitro studies. In the most comprehensive study presented so far, Amphotericin B was the most active antifungal agent with the majority of strains displaying Mucormycosis near the suggested breakpoint of $\leq$1 mg/mL.[28]

Surgical debridement has to be extensive, involving all necrotic areas for rhino-oculo-cerebral infection, and repeated this surgical procedure are recommended to achieve the local control and improve the outcome. For the pulmonary mucormycosis, the indication and timing of surgical management outside emergency care (hemoptysis) is still undefined.[27]

High dose liposomal amphotericin B as the therapy of choice for mucormycosis. Amphotericin B has manifest variable activity in vitro against agents responsible for mucormycosis. Liposomal amphotericin B is better tolerated and has lower toxicity.[9] Posaconazole gives helpful activity against the agents of mucormycosis. It compared with itraconazole and isavuconazole on a mg: mg basis, posaconazole has enhanced in vitro activity with reported 90% minimum inhibitory concentrations (MIC90) ranging from 1 to $\geq$ 4 mg/mL.[28]

Systemic administration of the medicament slows the infections and allows the control of the disease within the tissue, which cannot be resected. [29]

CONCLUSION

In conclusion, Mucormycosis is a life-threatening infection that most commonly affects immunocompromised individuals and that despite aggressive multimodal treatment carries a significant risk

of mortality. Findings from this review have helped ascertain the association between various manifestations of mucormycosis, their causative organism and respective types.

Thus it serves as a challenge to many clinicians. So by keeping its high mortality rate in mind, success to treat this infection efficiently lies within early and prompt diagnosis, attempt for recovery from the predisposing factors. With early intervention with surgical debridement and therapeutic drugs condition of this deadly disease can also be improved. COVID-19 is associated with a significant incidence of secondary infections, both bacterial and fungal probably due to immune dysregulation

A high index of suspicion is required in order to begin the appropriate diagnostic workup and treatment.

REFERENCES

1. Anna Skida, IoannisPavleas, Maria Drogari-Apiranthiou. (Epidemiology and Diagnosis of Mucormycosis: An Update), 2020; 6: 265.
2. V. SAEGEMAN, J. MAERTENS, N. ECTORS, et al. (Epidemiology of mucormycosis: review of 18 cases in a tertiary care hospital), 2010; 48: 245-254.
3. U. Binder, E. Maurer, C. Lass-Florl (Mucormycosis – from the pathogens to the disease), 2014; 20: 60-66.
4. Ashraf S. Ibrahim, Brad Spellberg, Thomas J. Walsh, et al. (Pathogenesis of Mucormycosis), 2012; 54(S1): S16-22.
5. Carlos Rodrigo Camara-Lemarroy, Emmanuel Irineo González-Moreno, René Rodríguez-Gutiérrez, et al. (Clinical Features and Outcome of Mucormycosis), 2014; 562610.
6. A. Skiada, C. Lass-Floerl, N. Klimko, et al. (Challenges in the diagnosis and treatment of mucormycosis), 2017; 56: S93–S101.
7. Jenish Bhandari, Pawan K. Thada, ShivarajNagalli. (RhinocerebralMucormycosis) 2021; http://creativecommons.org/licenses/by/4.0/
8. R. M. Prabhu, R. Patel (Mucormycosis and entomophthoramycosis: a review of the clinical manifestations, diagnosis and treatment), 2004; 10: 31–47.
9. E. Bouza, P. Mun˜oz, J. Guinea (Mucormycosis: an emerging disease?), 2006; 12: 7–23
10. Samir Kashyap, Jacob Bernstein, HammadGhanchi, et al. (Diagnosis of Rhinocerebral Mucormycosis by Treatment of Cavernous Right Internal Cartoid Artery Occlusion with Mechanical Thrmobectomy: Special Case Presentation and Literature Review), 2019; 10: 264.
11. Rishi Agrawal. MD, Anjana Yeldandi. MD, Hatice Savas. MD, et al. (Pulmonary Mucormycosis: Risk Factors, Radiologic Findings, and Pathologic Correlation), 2020; 40: 656–666
12. Francis Y.W. Lee, MD; Sherif B. Mossad, MD; Karim A. Adal, MD, MS (Pulmonary Mucormycosis), 1999; 159: 1301-1309.
13. Salwa O. Mekki, Amal A. Hassan, AfnanFalemban, et al. (Pulmonary Mucormycosis: A Case Report of a Rare Infection with Potential Diagnostic Problems) 2020; https://doi.org/10.1155/2020/5845394
14. XI-MING WANG, LING‑CHUAN GUO, SHENG‑LI XUE, et al. (Pulmonary mucormycosis: A case report and review of the literature), 2016; 11: 3049-3053.
15. Bianca Serio, Rosa Rosamilio, Valentina Giudice, et al. (Successful management of pulmonary mucormycosis with liposomal amphotericin B and surgery treatment: a case report), 2012; 43-47.
16. Haider A. Naqvi, Muhammad Nadeem Yousaf, Fizah S. Chaudhary, et al. (Gastric Mucormycosis: An Infection of Fungal Invasion into the Gastric Mucosa in Immunocompromised Patients), 2020; https://doi.org/10.1155/2020/8876125
17. Brad Spellberg, MD (Gastrointestinal Mucormycosis: An Evolving Disease), 2012; 140-142.
18. Ana Daniela Castrejón-Pérez, Esperanza C. Welsh, Ivett Miranda, et al. (Cutaneous mucormycosis), 2017; 92(3): 304-11.
19. SébastienMenzingera, Sabah Sid ‘Amar, GürkanKayaa, (Cutaneous Mucormycosis Resulting from Hematogenous Dissemination of Rhizomucorpusillus in an Immunocompromised Patient), 2020; 6: 275–278.
20. Robin Kaushik (Primary Cutaneous Zygomycosis in India) 2012; Indian J Surg, (November–December 2012); 74(6): 468–475.
21. Deepak Garg. ValliappanMuthu. Inderpaul Singh Sehgal, et al. (Coronavirus Disease (Covid-19) Associated Mucormycosis (CAM): Case Report and Systematic Review of Literature), 2021; 186: 289–298.
22. Sandeep Singh Awal, SomSubhro Biswas, Sampreet Kaur Awal (Rhino-orbital mucormycosis in COVID-19 patients—a new threat?), 2021; 52: 152.
23. Satvinder Singh Bakshi, Vinoth Kumar Kalidoss (COVID 19 infection and mucormycosis—a dangerously increasing combination), 2021; 37: 53.
24. Rimesh Pal, Birgurman Singh, Sanjay Kumar Bhadada, et al. (COVID-19-associated mucormycosis: An updated systematic review of literature) 2021; Mycoses, 2021; 00: 1–8.
25. Chelsea Guymer, Sanjeev Khurana, Ram Suppiah, et al. (Successful treatment of disseminated mucormycosis in a neutropenic patient with T-cell acute lymphoblastic leukemia), 2013. doi:10.1136/bcr-2013-009577.
26. Awadhesh Kumar Singh, Ritu Singh, Shashank R. Joshi, et al. (Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India), 2021.

https://doi.org/10.1016/j.dsx.2021.05.019 1871-4021.
27. Benoit Pilmis, Alexandre Alanio, Olivier Lortholary, et al. (Recent advances in the understanding and management of mucormycosis), 2018. doi: 10.12688/f1000research.15081.1.
28. Anna Skiada, Fanny Lanternier, Andreas H. Groll, et al. (Diagnosis and treatment of mucormycosis in patients with hematological malignancies: guidelines from the 3rd European Conference on Infections in Leukemia (ECIL3), 2012; 492-504.
29. SylwiaHnitecka, KamilNelke (RhinocerebralMucormycosis: Clinical Outcome, Diagnosis, Treatment – Review of the Literature), 2016; 536–541.