Xi'an Shiyou Daxue Xuebao (Ziran Kexue Ban)/
Journal of Xi'an Shiyou University, Natural Sciences Edition
ISSN: 1673-064X
E-Publication: Online Open Access
Vol: 66 Issue 07 | 2023
DOI 10.17605/OSF.IO/NZVGP

MUCORMYCOSIS IN ORAL & MAXILLOFACIAL REGION

HARIVIGHNESH S*
Postgraduate Trainee, Department of Oral and Maxillofacial Surgery, Tagore Dental College and Hospital, Chennai. Orcid: 0000-0002-8228-147X, Corresponding Author Email: drharivighnesh@gmail.com

RIAZ RAHIM
Professor and Head, Department of Oral and Maxillofacial Surgery, Tagore Dental College and Hospital, Chennai.

PANDIYARAJAN P
Postgraduate Trainee, Department of Oral and Maxillofacial Surgery, Tagore Dental College and Hospital, Chennai. Orcid: 0000-0002-7573-1727

ASHIK AHAMED
Postgraduate Trainee, Department of Oral and Maxillofacial Surgery, Tagore Dental College and Hospital, Chennai.

MOHAMMED HASSAIN Z
Postgraduate Trainee, Department of Oral and Maxillofacial Surgery, Tagore Dental College and Hospital, Chennai.

Abstract

Mucormycosis is an opportunistic, invasive fungal disease caused by mucormycetes. It is most common in highly immunocompromised hosts in developing countries. Absorption or inhalation of sporangiospores or inoculation of conidia by puncture trauma or wounds are the initial steps in the pathogenesis of mucormycosis. There are few high-quality reports on its implications in dental practice and Oral mucormycosis is usually caused by inhalation of spores or direct contamination of open oral wound. The most common form of this disease in maxillofacial region is rhino cerebral mucormycosis, with widespread involvement of oral cavity, maxilla, palate, nose, paranasal sinuses, orbits and central nervous system. Failure of prompt medical and surgical intervention may lead to cerebral spread, cavernous sinus thrombosis, septicemia and multiple organ failure lending to high morbidity and mortality .Amphotericin B is the drug of choice in mucormycosis. Supportive therapy includes; fluid balance, nutritional supplements and correction of underlying immune deficiency. Surgical management included combination of one or more procedures like tissue debridement, maxillectomy, sinus exploration and curettage. Newer drugs, adjuvant therapy like iron chelators and hyperbaric oxygen therapy has also been reported for treatment of mucormycosis.

Keywords: Amphotericin B, Dental Practice, Maxillofacial Region, Oral Mucormycosis, Surgical Management.

1. INTRODUCTION

Mucormycosis is an opportunistic, invasive fungal disease that most commonly affects patients with a morbidity history. COVID-19, a novel coronavirus, can be a risk factor for secondary fungal infections, which may or may not be associated with preexisting morbidities such as Diabetes Mellitus, HIV-associated malignancy, Haematological disorders, Prolonged steroid, and Antibiotic therapy. Even if diabetic patients are not infected with COVID, inadequate healthcare delivery systems put them at risk of

Xi'an Shiyou Daxue Xuebao (Ziran Kexue Ban)/
Journal of Xi'an Shiyou University, Natural Sciences Edition
ISSN: 1673-064X
E-Publication: Online Open Access
Vol: 66 Issue 07 | 2023
DOI 10.17605/OSF.IO/NZVGP

uncontrolled hyperglycemia and becoming prone to disease. Fungal osteomyelitis is most commonly found in people over 40 and more common in men. Rhino-cerebral, the most common form of this disease in the craniofacial area, is mucormycosis, which affects the oral cavity, maxilla, palate, zygomatic arch, pterygoid plates, paranasal sinuses, orbital region, and brain.

2. ABOUT MUCORMYCOSIS

The reported global prevalence of mucormycosis ranges from 0.005 to 1.7 per million population; however, the prevalence in India is nearly 80 times higher than in developed countries [4, 5, 6]. Diabetes is still the leading cause of mucormycosis worldwide, with a 46% mortality rate in diabetic patients who develop this fungal infection [7]. Diabetes is becoming more common in low- and middle-income countries. In 2011, 61.3 million Indian adults aged 20 to 79 years had diabetes, and this figure was expected to rise to 101.2 million by 2030 [8]. Diabetes prevalence is expected to rise significantly in China, Brazil, Japan, Mexico, Egypt, and Indonesia. As a result, the number of cases will likely rise in mucormycosis.

Furthermore, the world is still grappling with the COVID-19 pandemic, and there are few high-quality reports on its implications in dental practice [9]. Mucorales spores are likely to germinate quickly in COVID-19 infection patients, possibly due to low oxygen levels (hypoxia), high glucose levels (diabetes, new-onset hyperglycemia, and steroid-induced hyperglycemia), acidic medium, high iron levels, and decreased phagocytic activity of white blood cells [10]. The risk of mucormycosis increases in uncontrolled diabetes mellitus [11]. As a result, mucormycosis appears to be at the crossroads of two crises, COVID-19 and uncontrolled diabetes, in the context of the pandemic.

In a systematic review of all cases of mucormycosis documented in COVID-19 patients up to April 9, 2021, John et al. [11] identified 41 confirmed cases in COVID-19 patients, noting that 93% had diabetes and 88% were on corticosteroids. A second systematic review conducted after the first found a nearly three-fold increase in the number of published cases of mucormycosis in COVID-19 patients, with 82 cases (81.2%) reported in India, nine (8.9%) reported in the United States, three (3.1%) reported in Iran, and 19 (18.8%) reported in other countries [10]. In the same study, men outnumbered women (78.9%) among those with active (59.4%) or resolved (40.6%) COVID-19 infection. The nose and sinuses were the most commonly affected site (88.9%), followed by rhino-orbital mucormycosis (56.7%) and rhino-orbital-cerebral mucormycosis (22.2%) [11].

When possible, early and complete surgical treatment for mucormycosis is recommended, in addition to antifungal medications and correction of underlying predisposing factors [12]. Given the increasing number of cases and the predominance of orofacial involvement, we expect to see more patients with orofacial defects following surgical treatment for mucormycosis during the current COVID-19 pandemic. So, there is an urgent need to provide maxillofacial prosthetic rehabilitation for mucormycosis patients

Xi'an Shiyou Daxue Xuebao (Ziran Kexue Ban)/
Journal of Xi'an Shiyou University, Natural Sciences Edition
ISSN: 1673-064X
E-Publication: Online Open Access
Vol: 66 Issue 07 | 2023
DOI 10.17605/OSF.IO/NZVGP

to improve their quality of life. Dental and medical professionals must also be more aware of the morbidity associated with this condition.

Healthcare systems are overburdened due to the massive number of infected cases caused by COVID-19. Self-isolation causes metabolic decompensation, resulting in unmonitored hyperglycemia, which can lead to complications such as diabetic retinopathy, neuropathy, cardiovascular disease, and secondary bacterial and fungal infections such as rhinocerebral mucormycosis and staphylococcus sepsis, among others. [10]

Fever, headache, nasal or sinus congestion, swelling on one side of the face, black lesions on the nasal bridge, and upper hard palate inside the mouth are all symptoms of Rhinomaxillary Mucormycosis. In addition, failure to receive appropriate medical and surgical treatment may result in orbital involvement via the ethmoidal air sinuses and nasolacrimal duct and causes Rhino orbital Mucormycosis, which may lead to cerebral spread via the central retinal artery and cause Rhino-cerebral Mucormycosis, cavernous sinus thrombosis, sepsis, and multisystem organ failure, all of which cause significant morbidity and mortality [11].

Rhinomaxillary Mucormycosis is distinguished radiographically by paranasal sinus obliteration, erosion, and mucosal thickening of sinuses [12]. Mucormycosis is definitively diagnosed through tissue biopsy, which reveals hyphae of considerable size (5-30 microns), non-septate, thin wall, branched at right angles with the appearance of ribbon, and extensive necrosis of tissues [13]. According to Ahamed and Al Thobaiti, Multimodal treatment includes preexisting morbidity conditions, intensive antifungal therapy, and, most importantly, surgical care. [14]

Amphotericin B has long been used to treat Mucormycosis. However, according to a recent article, Muthu et al. emphasized the importance of liposomal Amp-B given at 3 mg/kg/day being equally efficacious and safer than the 10 mg/kg/day dose of Amphotericin-B drug due to its vasoocclusive nature. [15, 16] Currently, the novel drug regimen consists of liposomal Amphotericin B combined with either Itraconazole or Echinocandin.

Surgical care is critical, and debridement of all diseased and necrotic tissues should be performed as soon as possible, depending on disease progression. Surgical management combines partial or total maxillectomy, functional sinus endoscopic surgery, and curettage. [17, 18] If the orbital region is infected with a fungal infection, orbital exenteration can save your life. Hyperbaric oxygen therapy and iron chelating agents have also been reported to aid in forming granulation tissue and bone healing in treating Mucormycosis. [19, 20]

Xi'an Shiyou Daxue Xuebao (Ziran Kexue Ban)/
Journal of Xi'an Shiyou University, Natural Sciences Edition
ISSN: 1673-064X
E-Publication: Online Open Access
Vol: 66 Issue 07 | 2023
DOI 10.17605/OSF.IO/NZVGP

3. TREATMENT APPROACHES

3.1. Correction of the Underlying Disease

Treatment of mucormycosis requires removing the risk factors. Two risk factors were linked to a higher risk of mortality. Controlling hyperglycemia is crucial in cases of underlying DM, especially in cases of ketoacidosis. It is best to taper off corticosteroids and other immunosuppressive medications gradually. [21]

3.2. Antifungal Treatment

Guidelines for treating mucormycosis were released by the European Conference on Infections in Leukemia (ECIL) in 2017 and updated by the European Confederation of Medical Mycology (ECMM) in 2019. For adults, both societies strongly advise liposomal Amphotericin B (L-AmB) as the initial course of treatment. According to ECIL, another lipid formulation called Amphotericin B lipid complex (ABLC) could treat mucormycosis without affecting the central nervous system (CNS). L-AmB and ABLC were strongly advised as first-line treatments for infants and children. Liposomal amphotericin B has successfully treated mucormycosis with various organ involvement patterns in several case series. The daily doses varied between 1 mg/kg and 10 mg/kg. Increased dose recipients frequently experienced higher response rates. Significant and reversible increases in serum creatinine were seen in 104 patients receiving 10 mg/kg daily. Blood concentrations did not increase at doses greater than 10 mg/kg daily. Animal models and the observations above support liposomal amphotericin B 10 mg/kg per day in CNS involvement. Amphotericin B lipid complex 5 mg/kg per day has been used successfully when there is no CNS involvement. Amphotericin B lipid complex 10 mg/kg per day has been administered to kidney transplant patients. For many years, Amphotericin B deoxycholate has been the drug of choice. Although it works, its use is constrained by its high level of toxicity, particularly at the doses and for the lengths of time required to treat mucormycosis. Therefore, Amphotericin B deoxycholate should only be used when no other antifungal treatment is available.

The novel triazole isavuconazole, which comes in oral and intravenous formulations, exhibited at least some activity against various Mucorales strains. In a recent open-label phase 3 study, 37 cases of mucormycosis were examined (21 patients were receiving primary therapy, 11 had refractory disease, and 5 had intolerance). The overall response rate was 31%, the primary treatment group's response rate was 32%, and the patients who had previously failed other antifungal treatments had a 36% response rate. On day 180, the survival rate was 0.53, consistent with AmB and posaconazole published data.

Recommendations: Isavuconazole is highly recommended as a last resort. Posaconazole delayed-release tablets or infusions are strongly recommended over posaconazole oral suspension, which is only moderately recommended for salvage treatment when available. The guideline group supports recommendations for all three lipid-based amphotericin B formulations with strong to moderate strength in cases of primary treatment failure with isavuconazole or posaconazole. [22]

Xi'an Shiyou Daxue Xuebao (Ziran Kexue Ban)/
Journal of Xi'an Shiyou University, Natural Sciences Edition
ISSN: 1673-064X
E-Publication: Online Open Access
Vol: 66 Issue 07 | 2023
DOI 10.17605/OSF.IO/NZVGP

3.3. Combination Therapy

The majority of combination studies use either an echinocandin or AmB. One small retrospective study found that patients with ROC mucormycosis who received combined therapy with AmB and caspofungin, as opposed to AmB monotherapy, had better outcomes, particularly in cases of cerebral involvement. [22, 23]

3.4. New Drugs

Rezafungin, SCY-078, orolofim, and encochleated amphotericin B are a few new antifungal medications currently undergoing clinical evaluation. The new echinocandin Rezafungin has yet to be tested on Mucorales. A new subclass of glucan synthase inhibitors, SCY-078, has poor or no activity against Mucorales. Olorofim is a member of the new antifungal class known as orotomides. It works by inhibiting DHODH, a crucial enzyme in the biosynthesis of pyrimidines. Additionally, it has a meagre anti-Mucorales effect. Amphotericin B has a new oral formulation called encochleated amphotericin B. There is evidence that it is well tolerated. [23]

3.5. Hyperbaric oxygen (HBO)

The growth of Mucorales is inhibited in vitro by high oxygen concentration. According to a review on the use of HBO by John et al., it may be helpful for diabetic patients (94% survival), but its value for HM and HSCT patients is debatable (33% survival). Overall, the evidence is insufficient to support a suggestion that HBO is used frequently in mucormycosis. [23]

3.6. Surgery

Surgery is still simpler to perform in localizations of the rhino-orbital or cutaneous system than in the cerebral, pulmonary, or disseminated systems. Surgery was performed on 65.2% of 184 patients in a clinical-epidemiological review conducted over ten years, but only on 21.4% of patients with haematological conditions. Medical therapy alone had a worse outcome than medical therapy combined with surgical debridement. The availability of only retrospective studies and epidemiological data must be noted. However, the advantages of surgery are generally assumed and are strongly advised. [23, 24]

3.7. Adjunctive therapies

Iron chelators have been tried as an adjunctive therapy to lower iron availability and stop the growth of fungi. The incidence of mucormycosis has been linked to the iron chelator deferoxamine. The two other iron chelators, deferiprone and deferasirox, do not have the same xenosiderophoric properties as deferoxamine. Several authors have shown deferiprone to protect diabetic mice from mucormycosis. In neutropenic and diabetic mice, Deferasirox had the same impact and worked in concert with AmB. L-AmB, micafungin, and deferasirox triple therapy were also successful. A neutropenic mouse model's PSZ activity was elevated by deferasirox. These encouraging findings prompted a clinical trial to evaluate the effectiveness of deferasirox + LAmB. The mortality rate for

Xi'an Shiyou Daxue Xuebao (Ziran Kexue Ban)/
Journal of Xi'an Shiyou University, Natural Sciences Edition
ISSN: 1673-064X
E-Publication: Online Open Access
Vol: 66 Issue 07 | 2023
DOI 10.17605/OSF.IO/NZVGP

mucormycosis patients receiving deferasirox plus L-AmB was higher at 90 days than for those receiving L-AmB alone. Compared to the placebo group, deferasirox patients had higher rates of active malignancy, neutropenia, and corticosteroid therapy. There needed to be more sample size in the deferasirox and placebo groups to draw more definitive conclusions. In contrast to iron chelators, zinc chelators have demonstrated neither excellent nor lousy synergy with PSZ or AmB. [24]

3.8. New routes of administration

Nebulized antifungal medications could be a novel approach for research to enhance mucormycosis treatment. In particular, when AmB is used, local intrapulmonary drug delivery increases lung concentration with low systemic passage. An evaluation of the administration of L-AmB aerosol in a neutropenic mouse model of R. arrhizus pulmonary infection was conducted. From day 1 to day 5 after the challenge, aerosolized L-AmB was superior to placebo at reducing the fungal burden and enhancing survival. However, systemic L-AmB was not contrasted with aerosolized therapy. More research is required to evaluate aerosol efficacy both alone and in combination with systemic treatment. [24]

4. CONCLUSION

Rhino-orbital Mucormycosis has a better prognosis than other forms of Mucormycosis because early intervention in this area occurs. Although Mucormycosis caused by dental extraction is uncommon, it is on the rise in this COVID era and can result in severe morbidity and mortality. As a result, dental surgeons should be aware of the possibility of this severe complication in order to avoid an unsatisfactory clinical outcome. As a result, early detection and aggressive treatment, such as surgical debridement, can limit the spread of infection and reduce mortality.

References

1. Skiada A, Pavleas I, Drogari-Apiranthitou M. Epidemiology and diagnosis of mucormycosis: an update. J Fungi 2020; 6:265.
2. Prakash H, Chakrabarti A. Global epidemiology of mucormycosis. J Fungi 2019; 5:26.
3. Chander J, Kaur M, Singla N, Punia RPS, Singhal SK, Attri AK, et al. Mucormycosis: battle with the deadly enemy over a five-year period in India. J Fungi 2018; 4:46.
4. Jeong W, Keighley C, Wolfe R, Lee WL, Slavin MA, Kong DCM, et al. The epidemiology and clinical manifestations of mucormycosis: a system- atic review and meta-analysis of case reports. Clin Microbiol Infect 2019; 25:26-34.
5. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract 2010; 87:4-14.
6. Kazumichi Yonenaga et al Implications for clinical dental practice during the coronavirus disease pandemic: A scoping review
7. Singh AK, Singh R, Joshi SR, Misra A. Mucormycosis in COVID-19: a systematic review of cases reported worldwide and in India. Diabetes \& Metab Syndr Clin Res \& Rev 2021; 15:102146.

ISSN: 1673-064X
E-Publication: Online Open Access
Vol: 66 Issue 07 | 2023
DOI 10.17605/OSF.IO/NZVGP

8. John TM, Jacob CN, Kontoyiannis DP. When uncontrolled diabetes mellitus and severe COVID-19 converge: the perfect storm for mucormycosis. J Fungi 2021; 7:298.
9. Oliver A cornely et al, Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium doi: 10.1016/S1473-3099(19)30312-3.
10. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet. 2020; 395:1054-62.
11. Peterson K, Wang M, Canalis RF. Rhinocerebral mucormycosis: Evolution of the Disease and Treatment Options. Laryngoscope. 1997; 107:855-62.
12. Hudson JW. Osteomyelitis of the jaws: A 50-year perspective. J Oral Maxillofac Surg. 1993; 51:1294-301.
13. Urs A, Singh H, Mohanty S, Sharma P. Fungal osteomyelitis of maxillofacial bones: Rare presentation. J Oral Maxillofac Pathol. 2016; 20:546.
14. Ahamed SK, Al Thobaiti Y. Mucormycosis: A challenge for diagnosis and treatment-2 case reports and review of literature. Oral Health Dent Manag. 2014; 13:703-6.
15. Muthu V, Agarwal R, Dhooria S, Sehgal S, and Prasad K. Has the mortality from pulmonary Mucormycosis changed over time? A systematic review and meta-analysis. Clin Microbiol Infect. 2021; 27:538-49.
16. Spellberg B, Edwards J, Ibrahim A. Novel perspectives on mucormycosis: Pathophysiology, presentation, and management. Clin Microbiol Rev. 2005; 18:556-69.
17. Ribeiro NF, Wilson GE, Cousin CS, Butterworth DM, Wood wards TM. Lethal invasive mucormycosis: Case report and recommendations for treatment. Oral Maxillofac Surg. 2001; 30:156-9.
18. Tryfon S, Stanopoulos I, Kakavelas E, Nikolaidou A, Kioumis L. Rhinocerebral mucormycosis in a patient with latent diabetes mellitus: A case report. J Oral Maxillofac Surg. 2002; 60:327-30.
19. Hoenigl M, Gangneux JP, Segal E, Alanio A, Chakrabarti A, Chen SC, et al. Global guidelines and initiatives from the European Confederation of Medical Mycology to improve patient care and research worldwide: New leadership is about working together. Mycoses. 2018; 61:885-94.
20. Jenks JD, Salzer HJ, Prattes J, Krause R, Buchheidt D, Hoenigl M. Spotlight on isavuconazole in the treatment of invasive aspergillosis and mucormycosis: Design, development, and place in therapy. Drug Des Devel Ther. 2018; 12:1033-44.
21. Skiada A, LassFloerl C, Klimko N, Ibrahim A, Roilides E, Petrikkos G. Challenges in the diagnosis and treatment of mucormycosis. Med Mycol. 2018; 56:93-101.
22. Joerg J. Vehreschild, Andrea Birtel, Maria J. G. T. Vehreschild, Blasius Liss, Fedja Farowski, Matthias Kochanek, Michal Sieniawski, Angela Steinbach, Kerstin Wahlers, Gerd Fätkenheuer, and Oliver A. Cornely Mucormycosis treated with posaconazole: review of 96 case reports. \
23. François Danion, MD1 Claire Aguilar, MD, PhD1 Emilie Catherinot, MD. Mucormycosis: New Developments into a Persistently Devastating Infection.
24. Brunet, K., & Rammaert, B. (2020). Mucormycosis treatment: recommendations, latest advances, and perspectives. Journal de Mycologie Médicale,