

AMPHOTERICIN B IN “MUCORMYCOSIS” – THE UNPRECEDENTED SURGE OF PANDEMICCelcy S.^{1*}, Bera Joseph¹, Monika Narayan¹, Nahid¹, Sreelakshmi K.G.¹ and L. Britto Duraisingh²¹Pharm D Interns, Department of Pharmacy Practice, Nandha College of Pharmacy, Erode, Tamil Nadu, 638052, India.²Clinical Pharmacist, Ganga Medical Centre Hospital, Coimbatore, Tamil Nadu, 641043, India.***Corresponding Author: Celcy S.**

Pharm D Interns, Department of Pharmacy Practice, Nandha College of Pharmacy, Erode, Tamil Nadu, 638052, India.

Article Received on 21/10/2021

Article Revised on 11/11/2021

Article Accepted on 30/11/2021

ABSTRACT**Purpose:** Rhino orbital cerebral mucormycosis and use of amphotericin B in times of existing covid-19 pandemic.**Aim:** The aim of the study is to collect and document the cases of post covid rhino-orbital cerebral mucormycosis and also to observe and analyze the usage of amphotericin B at our institution. **Method:** This is a prospective, observational study. It was carried out at the tertiary care hospital from May 2021- August 2021. All patients of biopsy- proven Rhino-orbital mucormycosis were enrolled in the study. A minimum of 15 days follow-up was done for each patient. During the course of intravenous Amphotericin B, were analyzed by framing a checklist.**Result:** Seven patients were seen with the mean age of years. The major risk factors included are COVID-19 positivity (100%) with concomitant steroid using (57.14%) and uncontrolled diabetes mellitus (71.42%). Intravenous Amphotericin B was given to all patients for an average 7 days. Six patients were stable and were alive on follow-up. Mortality was seen in one patient. **Conclusion:** Mucormycosis is a rare condition which can still be fatal .A combination of surgical debridement plus intravenous Amphotericin B therapy, is acceptable in the management and has less morbidity rate.**KEYWORDS:** Post-covid Mucormycosis, Amphotericin-B, Rhino-Orbital Cerebral Mucormycosis.**INTRODUCTION**

The pandemic of coronavirus disease 2019 (COVID-19) still remains on an upsurge trend. The second wave of this disease has led to fear in most of the countries, including India and some parts of the world has started experiencing the third wave. As there are no proper treatment guidelines or protocols available for this deadly infection, supportive care equipment's such as oxygen cylinders, ventilators and heavy use of steroids play a vital role in the management of COVID-19.^[1] In the middle of the second wave of pandemic, the patients are acquiring secondary infections such as mucormycosis which is also known as black fungus disease. Physicians are documenting a raising number of cases of mucormycosis among COVID-19 patients. COVID-19 patients are prescribed with large doses of steroids resulting in a dull immune system and are susceptible to mucormycosis. In addition, steroids can result in spiking blood sugar levels, which is challenging for patients with increased diabetes and the acidic environment which favors the fungal (Mucorales) growth.^[1,2] The occurrence of fungal infection has increased considerably over recent decades. The most common pathogen includes *Candida spp*, *Aspergillus spp* and *Cryptococcus*. Mucormycosis may be a rare, invasive and rapidly progressive infection caused by fungi within the *Mucorales*. Mucormycosis is classed in line with the

location of infection. Most cases are rhino cerebral mucormycosis, but cutaneous, pulmonary, gastrointestinal and disseminated infection such as as sinus, Sino-orbital, and rhino cerebral infection are caused by the Mucorales. As the traditional term of “rhino cerebral” mucormycosis does not speak about the critical involvement of the attention, the more comprehensive term would be rhino-orbital-cerebral mucormycosis (ROCM). The most common comorbid conditions of ROCM are DM, hematological malignancies, hematopoietic somatic cell transplantation, and solid organ transplantation. Sporangiospores are deposited within the nasal turbinate's and Para nasal sinuses in immunocompromised patients. Qualitative and quantitative abnormalities of neutrophils, monocytes and macrophages increase the chance for development of mucormycosis. Altered metabolism of iron is also a decisive factor in the pathogenesis of patients with diabetes mellitus who are at risk for ROCM.^[3] Angioinvasion with thrombosis and tissue necrosis is the main pathophysiology of human Mucorales infection. The ethmoidal sinus may be a critical site from which sinus mucormycosis may extend through the *lamina papyracea* into the orbit, extra ocular muscles, and *nervous opticus*. The brain may be sowed by invasion of the ethmoidal and orbital veins, which drain into the cavernous sinuses. Diplopia and ophthalmoplegia could

also be the earliest symptoms of sinus cavernous syndrome before changes are evident on diagnostic imaging modalities. Mucormycosis of the maxillary sinus has an array of clinical features that are different from that of ethmoid sinus mucormycosis. A painful black necrotic ulceration may develop on the surface, indicating extension from the sinus into the mouth. Orbital apex syndrome is a forbidding complication of mucormycosis. Once within the orbital compartment, organisms may extend posteriorly to the optic foramen, where the ophthalmic artery, ophthalmic nerve and optic nerve are endangered by invasion, edema, inflammation and necrosis. Early diagnosis of sinus mucormycosis is very important for prevention of extension to orbital and cerebral tissues.^[3,6]

Surgical debridement in patient with rhino cerebral mucormycosis proceeds quickly because the field almost bloodless. Debridement is guided by CT or MRI images. Amphotericin B is the only drug available that is effective in mucormycosis. The dose of amphotericin B is limited by its renal toxicity therefore, amphotericin B includes a liposomal form of the drug the substance is effective and less toxic than conventional compound.^[4]

Liposomal amphotericin B in initial dose of 5mg/kg body weight (10mg/kg body weight in case of CNS involvement) it's a treatment of choice. Each vial contains 50mg. it should be diluted in 5% or 10% dextrose; it is compatible with normal saline or ringer lactate. It has to be continued till a positive response is achieved and disease is stabilized which can take several weeks following which step right down to oral posaconazole (300mg twice a day on first day and followed by 300mg OD) or isavuconazole (200mg 1 tablet thrice a day for two days followed by 200mg daily) Conventional amphotericin B in the dose of 1-1.5mg/kg may be used if liposomal form is not available and renal function and serum electrolytes are within normal limits. Another important formulation of Amphotericin B includes Amphomul which is oil in water emulsion. It is less toxic when compared to an oligomer form contained in conventional formulation. In this study we are observing the various infusions and issues related to Amphotericin B.^[6,7]

MATERIALS AND METHODS

This is a prospective observational study which was carried out at Tertiary care hospital from May 2021 to August 2021. In this study 7 patients with rhino orbital cerebral mucormycosis were involved. This study involved only the patients with Rhino orbital cerebral mucormycosis. A complete history taking, ophthalmological examination and imaging studies were done to the patients. The treatment approach was with intravenous amphotericin B (three different forms) and debridement of local necrotic tissue. Exenteration was done when indicated. A minimum of 15 days follow-up was done for each patient. During the course of the treatment different formulations of Amphotericin B were

analysed by framing a checklist containing required information during the administration of amphotericin B which was inserted into all cases. Each administration of amphotericin B must be done by filling the required details in the checklist. At the end of the treatment course we analysed the maximum used, most effective affordable, with minimal ADR formulations. Apart from this a multi-centric survey was conducted to study and evaluate the usage and problems associated with the infusion of amphotericin B in mucormycosis. Medicos from various institutions were participated in the survey and they responded with their experiences during the period of mucormycosis. These particulars guided us to draw a close.

RESULTS AND DISCUSSION

Mucormycosis may be a serious, aggressive and potentially fatal mycosis caused by a kind of rare but opportunistic fungal pathogen called mucormycetes and its recently referred to as Black fungus. There are multiple views regarding the present mucormycosis in India. The fungal disease is more prevalent in co-morbid conditions.^[5] The results are set out in the accompanying tables (1-5). The mean age was 38.2 years and commonly Male (85.07%) was more prone to the infection (table no.1). The maxillary region (100%) was the most affected part and other regions affected are sphenoid (42.85%), ethmoid (28.57%) and frontal (28.57%)(table no.3). The major threats included are covid positivity (100%), diabetes mellitus (71.42%), & concurrent steroid use (57.14%) (Table no.2). The duration of covid-19 positivity to the presentation of mucormycosis was on average of 2-3 weeks. Two uncontrolled type II diabetes mellitus and one had newly diagnosed diabetes mellitus at the time of mucormycosis. 3 patients had an average of 6 years of diabetes mellitus. The average value of HbA1c of these patients was found to be 9%. Diabetic cause abnormality of the immune response that fails to manage the spread of invading pathogens. Covid-19 tends to worsen diabetes and also cause diabetes in previously normal individuals.^[8] Mucor infection may occur during Covid-19 infection or a couple of weeks after recovery. It causes a decrease in some types of WBC and a decrease in immunity. Some medicines like steroids used for the treatment of Covid-19 infection can worsen immune status. The severity of Mucor infection is essentially hooked in to the patient's immunity and general health. If Covid-19 infection, high blood sugar level and immunosuppressive treatment are all present then the risk from infection increases.^[7,9] The most common clinical presentation was Headache (55%), Watery eyes (25%), Periorbital edema (35%), Nasal regurgitation (45%) & tooth ache(15%). The patients were treated with different formulations of amphotericin B according to the availability. The average duration for the infusion of IV amphotericin B conventional was 15 days, liposomal was 3 days and the emulsion was 5 days. The number of patients

with their own medication of amphotericin B was found to be 3. The adverse effects associated with the infusion of amphotericin B was found to be fever and chills (85.71%), hypokalemia (71.42%), renal toxicity (57.14%), desaturation and tachycardia (28.57%) and hepatotoxicity (14.28%)(Table no.5). Hypokalemia was managed with intravenous and oral potassium supplements. Medication and surgical debridement was the most preferred treatment option seen in this Centre as the first line. Amphotericin B injection followed by a switch over to Posoconazole as medications and surgical debridement of the affected part. Debridement was done in all seven patients (Table no.4). Exenteration was required in two patients. Early surgical infected of the infected sinuses and relevant debridement of the retro-orbital space can often prevent the infection from extending into the eye. Repeated surgical debridement may be necessary to make sure that all necrotic tissue has been debrided and the infection has not developed. 6 patients recovered during the study period and death occurred in one patient due to the diabetic ketoacidosis.

Table no 1: Epidemeology.

AGE	No. of cases
30 – 45	3 (42.85%)
45 – 55	2 (28.57%)
>55	2 (28.57%)
GENDER	
Male	6 (85.71%)
Female	1 (14.28%)

Table no 2: Risk Factors.

RISK FACTORS	No. of cases
Diabetes mellitus	5 (71.42%)
Covid positivity	7 (100%)
Hypertension	1 (14.28%)
Kidney disease	2 (28.57%)
HIV	1 (14.28%)
Intravenous steroids	4 (57.14%)
Post covid pneumonia	1 (14.28%)
Epilepsy	1 (14.28%)

Table no 3: Areas Involved.

Area involved	No. of cases
Sphenoid	3 (42.85%)
Ethmoid	2 (28.57%)
Maxillary	7 (100%)
Frontal	2 (28.57%)

Table no 4: Treatment.

Treatment	No. of cases
Medication and Debridement	4 (57.14%)
Medication, Debridement and Exenteration	3 (42.85%)

Table no 5: Amphoterecin-B Usage.

Formulation	No. of cases
Conventional	3 (42.85%)
Lipid-emulsion	4 (57.14%)
Liposomal	5 (71.42%)
Adverse effects	
Fever and chills	6 (85.71%)
Hypokalemia	5 (71.42%)
Renal toxicity	4 (57.14%)
Desaturation and tachycardia	2 (28.57%)
Hepatotoxicity	1 (14.28%)

CONCLUSION

There should be a high indication of speculation of rhino orbital mucormycosis in covid-19 epoch, in all patients they are presented with the involvement of areas such as Para nasal sinuses and the orbit with history of concurrent and controlled diabetes mellitus. It is important to recognize this infection at an initial stage to potentially reduce soft and hard tissue necrosis and severe complications and management with appropriate and aggressive antifungals and surgical debridement can improve survival.

REFERENCE

- Vishal U.S, Gururaj Arakeri, Gaurav Madikeri, Ashwin Shah et.al., COVID – 19 associated mucormycosis (CAM) in India: a formidable challenge. *British Journal of Oral and Maxillofacial Surgery*, 2021; 59(9): 1095-1098.
- Manjusha Nambiar, Sudhir Rama Varma, Marah Damdoun. Post-Covid alliance-mucormycosis, a fatal sequel to the pandemic in India. *Saudi Journal of Biological Sciences*, 2021; 28(11): 6461-6464.
- A. Mallis, S.N. Mastronikolis, S.S. Naxakis, A.T. Papadas. Rhinocerebral Mucormucosis: an update. *European Review for Medical and Pharmacological Sciences*, 2010; 14: 987-992.
- Sen M, Lahane S, Lahane TP, Parekh R, Honavar SG. Mucor in a viral land: A tale of two pathogens. *Indian Journal of Ophthalmology*, 2021; 69: 244–252.
- Zarpak L., Chirico F., Pruc M., et al. Mucormycosis — a serious threat in the COVID-19 pandemic? *Journal of Infection*, 2021; 83: 237–239.
- Mehta S, Pandey A. Rhino-Orbital mucormycosis associated with COVID-19. *Cureus*, 2020; 12: e10726. doi: 10.7759/cureus.10726
- Vishal U.S.Rao, Gururaj Arakeri, Gaurav Madikeri et al., Covid-19 associated mucormycosis (CAM) in India: a formidable challenge. *British Journal of Oral Maxillofacial Surgery*, 2021; 6(13).
- Ravani S.A., Agrawal G.A., Leuva P.A., et al. Rise of the phoenix: mucormycosis in COVID-19 times. *Indian Journal Ophthalmology*, 2021; 69: 1563–1568.
- Nithyanandam S, Jacob MS, Battu RR, Thomas RK, Correa MA, D'Souza O. Rhino-orbito-cerebral mucormycosis. A retrospective analysis of clinical

- features and treatment outcomes Indian Journal of Ophthalmology, 2003; 51: 231–236.
10. Shah K, Dave V, Bradoo R, Shinde C, Prathibha M. Orbital exenteration in rhino-orbito-cerebral mucormycosis: A prospective analytical study with scoring system. Indian Journal Otolaryngology Head Neck Surgery, 2019; 71: 259–265.
 11. Mathebula SD. Mucormycosis. South African Optometrist, 2008; 67(1): 36–41.