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Original Research Article

Study of mucormycosis patients attending tertiary care hospital: a retrospective study

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ABSTRACT

Background: Treatment of mucormycosis involves a combination of surgical debridement of involved tissues and antifungal therapy. Intravenous amphotericin B is the drug of choice. In this study authors assessed the outcomes of treating patients with mucormycosis with varied formulations of amphotericin.
Methods: Authors performed a retrospective observational study of patients diagnosed with mucormycosis and admitted in the inpatient ward of Bharati Hospital, Sangli, Maharashtra, India from May 2015 till May 2018. Patients either received amphotericin B, lyophilized amphotericin B or lipid soluble amphotericin B. Resolution of symptoms was graded as good clinical response and persistence of symptoms as poor clinical response.
Results: During the study period a total of 16 patients were included in the study. All patients underwent surgical debridement and received different forms of amphotericin. Three patients received amphotericin B 1.5 to 3 grams over 21 days and responded satisfactory and later had renal toxicity. Five patients received lyophilized amphotericin B 3 to 4 grams over 21 days, with good response and less renal toxicity as compared to amphotericin B. Lipid soluble amphotericin B was given to 8 patients 3.5 to 5 gm over 21 days with good clinical response and minimal renal toxicity. Of the 10 patients who presented with nasal discharge, 60% had a good clinical outcome, 30% had poor and one patient died.
Conclusions: Amphotericin B is an effective anti-fungal. Further studies are needed to assess the utility of immunologic and metabolomic profiling of the host and prescribing targeted immunotherapy in decreasing the incidence of mucormycosis.

Keywords: Amphotericin, Clinical outcome, Diabetes, Mortality, Mucormycosis

INTRODUCTION

Mucormycosis is manifested by a variety of different syndromes in humans, particularly in immunocompromised patients and those with diabetes mellitus.[1] Devastating rhino-orbital-cerebral and pulmonary infections are the most common syndromes caused by these fungi. Almost all patients with invasive mucormycosis have some underlying disease that both predisposes to the infection and influences the clinical presentation. The most common underlying diseases are diabetes mellitus, treatment with glucocorticoids, hematologic malignancies, hematopoietic stem cell transplantation, solid organ transplantation, iron overload, HIV and burns.[2] Treatment of mucormycosis involves a combination of surgical debridement of involved tissues and antifungal therapy. Elimination of predisposing factors for infection, such as hyperglycemia, metabolic acidosis, deferoxamine administration, and neutropenia, is also critical. Intravenous amphotericin B is the drug of choice. Most clinicians use a lipid formulation of amphotericin B in order to deliver a high dose with less

nephrotoxicity. Though liposomal amphotericin B is preferred as primary therapy, amphotericin B deoxycholate is still used in many patients in India due to its low cost. Though the general consensus exists regarding the duration of therapy, there is dearth of literature on mucormycosis from Indian cases, and authors therefore decided to study the outcomes of treating patients with mucormycosis with varied formulations of amphotericin at the centre.

METHODS

Authors performed a retrospective observational study of patients diagnosed with mucormycosis and admitted in the inpatient ward of Bharati Hospital, Sangli, Maharashtra, India from May 2015 till May 2018. Authors included all patients admitted with diagnosis of mucormycosis during the study period. The diagnosis of these patients was confirmed microbiologically and after histopathological testing. The diagnosis of mucormycosis was confirmed when broad aseptate/sparsely septate, ribbon like hyphae with right angled branching were demonstrated in tissue specimen or aseptically aspirated material from lesion with or without isolation of mucormycetes. Those patients with a clinical suspicion of mucormycosis but without mycology or histopathology confirmation were not included. Enrolled patients comprised both immunocompromised and immunocompetent individuals.

Statistical analysis

The medical history of the patients with mucormycosis was collected from the medical records regarding mode of presentation, previous medical history, treatment given, and response to treatment. Patients either received amphotericin B, lyophilized amphotericin B or lipid soluble amphotericin B, the choice of which was made by the treating physician in consultation with the patient. Resolution of symptoms was graded as good clinical response and persistence of symptoms as poor clinical response. Mortality was noted as well. Data were collected using a pre-designed case report form and frequency distribution tables were created.

RESULTS

During the study period a total of 16 patients were included in the study. All of them presented with nasal crusting (Table 1).

Table 1: Clinical features of the patients included in the study.

Modes of presentations	N
Nasal discharge	10
Nasal crusting	16
Palatal perforation/crusting	04
Orbital involvement (ophthalmoplegia/vision loss)	05
Intracranial involvement	02
Medical conditions	
Diabetes mellitus	16
Acute kidney injury/chronic kidney disease	14
HIV	00
Immunosuppressant therapy	01

Ten patients presented with nasal discharge, five with orbital involvement associated with ophthalmoplegia and/or vision loss, and two with intracranial involvement.

All of the them had a medical history of diabetes mellitus, 14 had a history of acute or chronic kidney disease. Only one was on immunosuppressant therapy. All patients underwent surgical debridement and received different forms of amphotericin (Table 2).

Three patients received amphotericin B 1.5 to 3 grams over 21 days. These patients responded satisfactory and later had renal toxicity. Five patients received lyophilized amphotericin B 3 to 4 grams over 21 days, with good response and less renal toxicity as compared to amphotericin B. Lipid soluble amphotericin B was given to 8 patients 3.5 to 5 gm over 21 days with good clinical response and minimal renal toxicity. Of the 10 patients who presented with nasal discharge, 60% had a good clinical outcome, 30% had poor and one patient died (Table 3).

Of the 16 patients who presented with nasal crusting, 50% had a good clinical outcome, 31% poor and 19% died. Among those with palatal perforation, only 25% had a good clinical outcome, 50% had poor outcome and one patient died. Among those with orbital involvement, one patient died, and one had a poor outcome, while three patients demonstrated a good clinical outcome, exenteration of the eye ball was done for patients with non-viable eye. Both the patients with intracranial involvement died despite the treatment given.

Table 2: Response to various types of amphotericin B given adjuvant to surgical debridement.

Type of amphotericin	N	Total dose	Response
Amphotericin B	3	1.5-3 grams over 21 days	Average response renal toxicity +
Lyophilized amphotericin B	5	3- 4 grams over 21 days	Good response renal toxicity comparatively less
Lipid soluble amphotericin B	8	3.5 - 5 grams over 21 days	Good response minimal renal toxicity

Table 3: Distribution of patients according to the clinical response to therapy.

Modes of presentation	Average dose of amphotericin given	Clinical outcome					
		Good		Poor		Death	
		N	%	N	%	N	%
Nasal discharge	3 grams	6	60 %	3	30 %	1	10 %
Nasal crusting	3.5 grams	8	50 %	5	31 %	3	19 %
Palatal perforation/crusting	4.5 grams	1	25 %	2	50 %	1	25 %
Orbital involvement (ophthalmoplegia/vision loss)	4.5 grams	3	60%	1	20%	1	20%
Intracranial involvement	5 grams	0	0%	0	0%	2	100%

DISCUSSION

Management of mucormycosis requires a multimodal approach. It includes reversal of underlying predisposing factors, discontinuation of factors resulting in immunocompromised state and early administration of active antifungal agents at the optimal dose, complete removal of all infected tissues and the use of various adjunctive therapies.[3] Corticosteroids and other immunosuppressive drugs should be tapered quickly and to the lowest possible dose. Early diagnosis is crucial in order to promptly initiate therapeutic interventions necessary for preventing progressive tissue invasion and its devastating sequelae, minimizing the effect of disfiguring corrective surgery, and improving outcome and survival.[4] Chamilos G et al, showed that delaying effective amphotericin B-based therapy in mucormycosis patients with hematological malignancies for more than 5 days resulted in an approximately twofold increase in 12-week mortality as compared to those who started treatment immediately.[5] In the present study, 16 patients were included with a diagnosis of mucormycosis and treated with different formulations of amphotericin B. Three patients received amphotericin B, five received lyophilized amphotericin B and eight lipid soluble amphotericin B.

Various risk factors are associated with the development of mucormycosis. All the patients in the present study had a medical history of diabetes mellitus, 14 had a history of acute or chronic kidney disease and one was on immunosuppressant therapy. Though not assessed in the present study, in uncontrolled diabetes, ketoacidosis is considered the key factor for predisposition to mucormycetes infection, as low serum pH diminishes the phagocytic effect of macrophages, chemotactic and oxidative burst of neutrophils. In a review of 179 cases of paranasal sinus mucormycosis by Diwakar et al, 70% of patients had diabetic ketoacidosis.[6] Chakrabarti A et al, reported diabetic ketoacidosis in 27.3% of the patients.[7] None of the patients in present study had any diagnosed malignancy. Among patients with malignancy, hematologic malignancies are much more frequently associated with mucormycosis than solid tumors.[8] However, even in patients with hematologic malignancies, mucormycosis appears to occur in fewer than 1% of patients.[9] Among hematopoietic cell transplant recipients, the reported incidence has ranged from 0.1 to 2%, with the highest incidence in patients with graft-versus-host disease.[10] Dose of amphotericin B is still debated. Comparative analysis of liposomal amphotericin and amphotericin lipid complex for the treatment of acute experimental invasive pulmonary mucormycosis in neutropenic mice demonstrated significant differences in the dose-dependent activities of the two lipid formulations.[11] These findings were consistent with the concept that the efficacies of antifungals for the treatment of mucormycosis are closely tied to the rapid loading of the target tissues with concentrations of drug sufficient to suppress fungal proliferation and reduce the potential for angioinvasion and subsequent dissemination. As a result, the authors suggested that different dosing approaches for liposomal and lipid soluble formulations may be required. The working group on Zygomycosis of the European confederation of medical mycology advocates the use of a lipid formulation of amphotericin B as first-line therapy for mucormycosis.[12] The suggested dose for liposomal amphotericin B is 5mg/kg/day and can be increased to 10mg/kg/day for infection of the central nervous system. In the Ambi Zygo study, performed by the French mycosis study group, patients received 10mg/kg/day of liposomal amphotericin B for the first month of treatment, in addition to surgical debridement, where required.[13] The overall response rate reported in the study was 36% at week 4 and 45% at week 12. Renal function impairment as shown by doubling of serum creatinine level was noted in 40% of patients. Treatment of mucormycosis with liposomal amphotericin B has been shown to be associated with a 67% survival rate, compared to 39% survival when patients were treated with amphotericin B ($p = 0.02$).[14] Multiple other case series also found initial therapy with liposomal formulation to be substantially more effective than other options.[15] The superiority of liposomal amphotericin was also demonstrated in diabetic keto-acidotic (DKA) mice infected with Rhizopus oryzae.[16]

CONCLUSION

Mucormycosis is although relatively rare, but poses an important burden on immunocompromised patients, due

to its persistently high mortality. The incidence seems to be increasing with the development of newer and more effective immunosuppressant agents. The present study highlights the need of further awareness about the disease and the need for aggressive measures for early diagnosis and management. The clinical presentation is nonspecific, which presents a diagnostic dilemma to the clinician. Amphotericin B is an effective anti-fungal but runs the risk of severe nephrotoxicity patients who are already diabetic or suffer from chronic debilitating diseases. Further studies are needed to assess the utility of immunologic and metabolomic profiling of the host and prescribing targeted immunotherapy in decreasing the incidence of mucormycosis.

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