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Case Report

Sino orbital mucormycosis treated with fluconazole

Assaye N. Alebachew*, Dawit K. Dibaba

Department of Otolaryngology Head and Neck Surgery, College of Health Sciences, Addis Ababa University, Ethiopia

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***Correspondence:**
Dr. Assaye N. Alebachew,
E-mail: assaye.nibret@aau.edu.et

ABSTRACT

The successful treatment of mucormycosis requires; early diagnosis; reversal of underlying predisposing risk factors, if possible, surgical debridement, where applicable and prompt antifungal therapy. Amphotericin B is the gold standard antifungal treatment against mucormycosis to date. However, there are newer agents described recently like posaconazole and isavuconazole which can be used as an option in a few instances. Although amphotericin B especially the liposomal preparation is the preferred agent, the availability and the cost limit its use, especially in resource-limited setups. Generally, azole drugs, especially the first generations such as fluconazole, are not effective against zygomycetes. However, few reports showed complete recovery after use of fluconazole for adjunct treatment. Here we report on a 35-year-old newly diagnosed diabetic woman with Sinoorbital mucormycosis who has been treated with surgical debridement and intermittent bases of amphotericin B and was discharged home without optimal response but returned completely improved after three months of oral fluconazole.

Keywords: Amphotericin B, Fluconazole, Invasive fungal sinusitis, Mucormycosis

INTRODUCTION

Mucormycosis is a life-threatening infection caused by fungi of the order Mucorales. The rhino-orbitocerebro presentation is said to be the most common, especially in patients with Diabetes mellitus.[1] Antifungal treatment, surgical debridement and reversal of the predisposing factor is the management standard. Amphotericin B, preferably lipid formulation, is thought to be the standard of antifungal treatment against mucormycosis in general.

However, there are newer agents like posaconazole which proved to be effective too.[2] Other triazoles, such as fluconazole, are said to be infective against invasive fungal rhinosinusitis in different in vitro studies. Although in vivo studies have not been performed, some reports indicate a positive outcome of the use of fluconazole in the treatment of invasive fungal rhinosinusitis.[3,4]

CASE REPORT

A 35-year-old newly diagnosed diabetic woman with treated diabetic ketoacidosis has been referred to our hospital after she had left-side nasal obstruction, facial swelling and skin darkening, palatal darkening, fever and orbital protrusion with complete visual loss of 3 weeks duration. She has been on broad-spectrum antibiotics and insulin, but not on any antifungal.

On physical examination, there was darkening of the mucosa with loss of sensation all over the septum (on both sides), nasal floor, turbinate, sphenoid rostrum, nasopharynx (including the opening of the eustachian tube) and ipsilateral hard palate (Figure 1). There was also a loss of cutaneous sensation along the infraorbital nerve distribution. Orbital examination showed periorbital edema with proptotic eyeball. The pupil was dilated with direct or consensual light reflex. Computed tomography shows features of chronic rhino sinusitis

except for air in the retromaxillary area and in the nasopharyngeal soft tissues. Serum inflammatory markers were increased (C-reactive protein-182 (reference: 0-5), erythrocyte sedimentation rate 90 (reference<20 mm/hr.). The diagnosis of Sino orbital mucormycosis was made. The patient started on intravenous amphotericin B, endoscopic clearance of the sinonasal cavity and the nasopharnyx was done. Additionally, a subtotal maxillectomy was performed. The biopsy result came with histological sections showing broad non-septated hyphae branching at 90 degrees and infiltrating the surrounding fibrosclerotic and bony tissues. Hematoxylin and eosin staining was performed as well as Periodic acid-Schiff (PAS) staining and the morphological findings were consistent with mucormycosis infection.

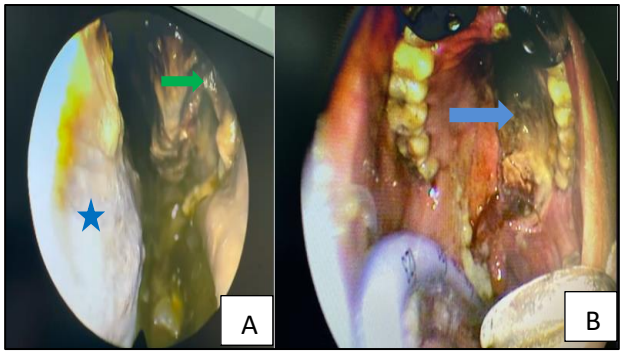

Figure 1 (A and B): Preoperative endoscopy. Star (nasal septum), green arrow (left middle turbinate), yellow arrow (hard palate mucosa).

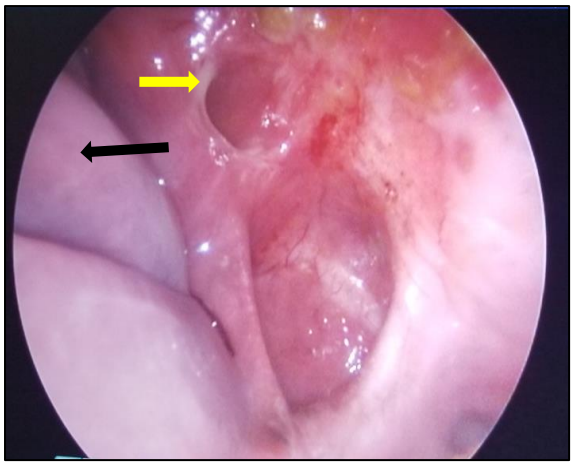

Figure 2: Six months after treatment. Yellow arrow (sphenoid sinus), black arrow (contralateral middle turbinate).

As the patient did not have satisfactory clinical and laboratory improvement, a revision of endoscopic clearance and orbital exenteration was performed two weeks after the initial surgery. The patient started to show significant clinical improvement, but it was not possible to maintain amphotericin B treatment due to the availability of the drug. After 3 months of on-and-off treatment with IV amphotericin B and suboptimal clinical and laboratory improvement, we decided to put the patient on oral fluconazole and send her home. After 3 months of 200 mg of oral fluconazole/day treatment, the patient arrived with complete clinical and laboratory recovery (Figure 2).

DISCUSSION

Mucormycosis is a life-threatening infection caused by fungi of the order Mucorales. Mucormycosis virtually always occurs in patients with host defense defects and / or increased available serum iron, although rare cases have been reported in apparently normal hosts. Based on the clinical presentation and the involvement of a particular anatomic site, mucormycosis can be divided into at least six clinical categories: (i) rhinocerebral, (ii) pulmonary, (iii) cutaneous, (iv) gastrointestinal, (v) disseminated and (iv) miscellaneous.[2] Patients with diabetics with ketoacidosis typically develop the rhino cerebral form of the disease and much more rarely develop pulmonary or disseminated disease.[1,5]

The clinical presentation in conjunction with the biopsy of the suspected tissue for pathology and culture is critical to make the diagnosis of invasive fungal rhino sinusitis. Inflammatory markers such as the C reactive protein are found to be of paramount importance for prognostication and treatment follow-up.[6] The mortality rate of mucormycosis has remained>40% despite aggressive surgical and antifungal therapy and is even more guarded in those patients whose underlying condition is irreversible.[7] The successful treatment of mucormycosis requires four steps: 1) early diagnosis; 2) reversal of underlying predisposing risk factors, if possible; 3) surgical debridement, where applicable; and 4) prompt antifungal therapy.

The antifungal drugs currently available against mucormycosis are limited in type and have variable in vivo and in vitro activity.[8] Generally, antifungal drugs can be classified based on their mechanism of action in five classes: polyenes, azoles, allylamines, echinocandins and other agents, including griseofulvin and flucytosine. Primary antifungal therapy for mucormycosis should be based on a polyene, if possible.[9] Both the conventional and its lipid formulations of amphotericin B are considered the drug of choice for the primary treatment of mucormycosis, although, as with many antifungal agents, the optimal dosage for amphotericin B and its formulations against mucormycosis is still undetermined.[8]

Unfortunately, its clinical use is hindered by intrinsic toxicity and the need for intravenous administration. Dose-dependent nephrotoxicity is frequently encountered with therapeutic doses.[10] The development of amphotericin B lipid preparations has substantially reduced, but not eliminated nephrotoxicity. This has given the advantage of delivering the drug in a higher

dose. Their main drawback is that they are substantially more expensive than conventional amphotericin B. Analysis carried out from the perspective of the Brazilian Public Health System showed that conventional amphotericin B is the most cost-effective treatment, followed by liposomal amphotericin B and amphotericin B lipid complex.[11] Following the polene group of antifungals, selected drugs in the azole group are used as the first line when amphotericin B formulations are not tolerated or as a salvage when those drugs are deemed to be ineffective. Second-generation triazoles, posaconazole and isavuconazole exhibit higher activity against Mucorales in vitro than other triazoles.[12]

In a single-arm open-label trial carried out in adult patients with invasive fungal disease caused by rare fungi, including mucormycosis, isavuconazole showed activity against mucormycosis with efficacy similar to amphotericin B and can be used for the treatment of mucormycosis and is well tolerated.[13] Although clinical studies on the efficacy of posaconazole for mucormycosis are scarce, early case reports and case series reported that posaconazole could be an option as salvage therapy in patients unresponsive or intolerant to liposomal amphotericin B. And this drug is generally well tolerated, except for minor gastrointestinal side effects due to its sole oral administration option.[14,15]

A case report on a diabetic child with rhinocerebral mucormycosis has shown complete recovery after the use of fluconazole instead of amphotericin B after he had an adverse reaction from it.[3] The same kind of response has been reported in a leukemic patient with pulmonary mucormycosis after the use of intravenous fluconazole.[4]

Generally, azole drugs, especially the first generations such as fluconazole, are not effective against zygomycetes. A study that assessed in-vitro activities of Posaconazole, Itraconazole, Voriconazole, Amphotericin B and Fluconazole (at different minimum inhibitory concentrations) against 37 clinical isolates of zygomycetes has found that the isolates were generally susceptible to Posaconazole, Itraconazole and Amphotericin B. However, most of the isolates were resistant to fluconazole. In general, most in vitro and in vivo animal studies have shown poor efficacy of azoles against mucormycosis.[16-18]

CONCLUSION

Although complete recovery for our patient could be due to improved immune status and neutrophil function, it is worth putting these patients on fluconazole when there are no other options such as amphotericin B, which is the standard antifungal against mucormycosis or second-generation triazoles such as Posaconazole and isavuconazole.

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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. Torres HA, Hachem RY, Chemaly RF, Kontoyiannis DP, Raad II. Posaconazole: a broad-spectrum triazole antifungal. Lancet Infect Dis. 2005;5(12):775-85.
3. Selcen D, Secmeer G, Aysun S, Kanra G, Onerci M, Gököz A, et al. Mucormycosis in a diabetic child and its treatment with fluconazole: a case report. Turk J Pediatr. 1995;37(2):165-8.
4. Funada H, Miyake Y, Kanamori K, Okafuji K, Machi T, Matsuda T. Fluconazole therapy for pulmonary mucormycosis complicating acute leukemia. Jpn J Med. 1989;28(2):228-31.
5. Spellberg B, Edwards J, Ibrahim A. Novel perspectives on mucormycosis: Pathophysiology, presentation and management. Clin Microbiol Rev. 2005;18(3):556-69.
6. Cho H-J, Jang M-S, Hong SD, Chung S-K, Kim HY, Dhong H-J. Prognostic factors for survival in patients with acute invasive fungal rhinosinusitis. Am J Rhinol Allergy. 2015;29(1):48-53.
7. Spellberg B, Ibrahim AS. Recent advances in the treatment of mucormycosis. Curr Infect Dis Rep. 2010;12(6):423-9.
8. Espinel-Ingroff A, Chakrabarti A, Chowdhary A, Cordoba S, Dannaoui E, Dufresne P, et al. Multicenter evaluation of MIC distributions for epidemiologic cutoff value definition to detect amphotericin B, posaconazole and itraconazole resistance among the most clinically relevant species of Mucorales. Antimicrob Agents Chemother. 2015;59(3):1745-50.
9. Sipsas N V., Gamaletsou MN, Anastasopoulou A, Kontoyiannis DP. Therapy of mucormycosis. J Fungi. 2018;4(3):1-17.
10. Espinel-Ingroff A. Antifungal Agents. Encycl Microbiol Third Ed. 2009;187(7):205-22.
11. Borba HHL, Steimbach LM, Riveros BS, Tonin FS, Ferreira VL, Bagatim BA de Q, et al. Cost-effectiveness of amphotericin B formulations in the treatment of systemic fungal infections. Mycoses. 2018;61(10):754-63.
12. Smith C, Lee SC. Current treatments against mucormycosis and future directions. PLoS Pathog. 2022;18(10):1-7.
13. Marty FM, Ostrosky-Zeichner L, Cornely OA, Mullane KM, Perfect JR, Thompson GR, et al. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. Lancet Infect Dis. 2016;16(7):828-37.

14. Vehreschild JJ, Birtel A, Vehreschild MJGT, Liss B, Farowski F, Kochanek M, et al. Mucormycosis treated with posaconazole: review of 96 case reports. Crit Rev Microbiol. 2013;39(3):310-24.
15. Greenberg RN, Mullane K, Van Burik J-A, Raad I, Abzug MJ, Anstead G, et al. Posaconazole as salvage therapy for zygomycosis. Antimicrob Agents Chemother. 2006;50(1):126-33.
16. Sun QN, Fothergill AW, McCarthy DI, Rinaldi MG, Graybill JR. In vitro activities of posaconazole, itraconazole, voriconazole, amphotericin B, and fluconazole against 37 clinical isolates of zygomycetes. Antimicrob Agents Chemother. 2002;46(5):1581-2.
17. Pfaller MA, Messer SA, Hollis RJ, Jones RN. Antifungal activities of posaconazole, ravuconazole and voriconazole compared to those of itraconazole and amphotericin B against 239 clinical isolates of Aspergillus spp. and other filamentous fungi: report from SENTRY Antimicrobial Surveillance Program, 2000. Antimicrob Agents Chemother. 2002;46(4):1032-7.
18. Gomez-Lopez A, Cuenca-Estrella M, Monzon A, Rodriguez-Tudela JL. In vitro susceptibility of clinical isolates of Zygomycota to amphotericin B, flucytosine, itraconazole and voriconazole. J Antimicrob Chemother. 2001;48(6):919-21.

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