Original Article

Management of rhinomaxillary mucormycosis with Posaconazole in immunocompetent patients

Sachin Rai^{*}, Shikha Yadav, Dinesh Kumar, Vijay Kumar, Vidya Rattan

Unit of Oral & Maxillofacial Surgery, Oral Health Sciences Centre, Postgraduate Institute of Medical Education & Research, Chandigarh 160012, India

ARTICLE INFO

Article history:

Received 4 September 2016

Accepted 10 October 2016

Available online 20 October 2016

Keywords:

Fungal osteomyelitis

Mucormycosis

Amphotericin B

Posaconazole

ABSTRACT

Mucormycosis is an opportunistic, uncommon and serious systemic fungal infection mostly presenting in immunocompromised patients. The combination of surgical debridement, parenteral therapy with Amphotericin B and management of the underlying systemic disease is the standard treatment modality for mucormycosis. The drawback of this regime is the need for long hospitalization due to the serious side effects of Amphotericin B requiring regular monitoring. Oral Posaconazole is one of the newer antifungals that have shown promising results. This paper highlights a case series of rhinomaxillary mucormycosis in immunocompetent patients diagnosed and managed successfully with surgical debridement and oral Posaconazole administration on out-patient basis.

© 2016 Craniofacial Research Foundation. All rights reserved.

1. Introduction

Mucormycosis is an opportunistic systemic fungal infection caused by order Mucorales. The pathogens are commonly found in the environment in the soil and decaying organic debris. Mucormycosis has been classified according to its clinical presentation into rhinocerebral, cutaneous, gastrointestinal, pulmonary and disseminated forms. The most common form is the rhinocerebral that has been further subclassified into rhinomaxillary, rhinocerebral and rhinoorbital types. Rhinomaxillary form presents with mobility of maxillary teeth, pus discharge along teeth or sockets, mobility of maxilla, palatal necrotic tissue or perforations, sinusitis and blackish mucous discharge from nostrils. Fungal spores enter the human body through inhalation hence the infection mostly presents itself in the nose and paranasal sinuses.¹ The fungus invades the blood vessels resulting in vascular thrombosis, which leads to ischemia and necrosis of tissue. Mucormycosis is uncommon in healthy individuals and usually appears in immunocompromised patients with conditions like uncontrolled diabetes, AIDS, hematological malignancies, renal failure and patients on chemotherapy or long term steroids.² Rarely it presents itself in immunocompetent patients.^{3,4} The

standard management of mucormycosis consists of aggressive debridement of the infected hard and soft tissue and parenteral antifungal therapy with Amphotericin B.⁵ Newer antifungal drugs like Posaconazole, Voriconazole and Itraconazole have been used against mucor with variable results and evidence.^{6,7} Amphotericin B is the gold standard for medical therapy of mucor but it needs hospitalization and monitoring due to its side effects.^{8–11} This paper presents a retrospective analysis of six immunocompetent patients of mucormycosis who were treated with surgical debridement and oral therapy with Posaconazole on outpatient basis. The aim is to highlight the efficacy of Posaconazole and to propose it as a first line drug in case of rhinomaxillary mucormycosis because of its ease of administration and minimal side effects.

2. Methodology

Six patients suffering from rhinomaxillary mucormycosis were retrospectively analyzed over a 3-year (2012–2015). Due to the retrospective nature of this study, it was granted an exemption in writing by the institute's ethical committee. The clinical features and the management have been described in Table 1. All the patients presented with common clinical features of spontaneous and painless loosening of maxillary teeth and bone with or without pus discharge and exposed maxillary bone (Fig. 1). Computerized tomographic scan of all patients showed typical features of partial or complete necrosed dentoalveolar segment separated from the basal maxillary bone with involvement of the maxillary sinus

^{*} Corresponding author.

E-mail addresses: drraisachin@gmail.com (S. Rai), drshikhayadav@gmail.com (S. Yadav), dr_dinesh78@yahoo.com (D. Kumar), vijaychd88@gmail.com (V. Kumar), drvidyarattan@gmail.com (V. Rattan).

Table 1

Clinical features and management of six immunocompetent patients.

Patient	Age/sex	Duration, presentation/chief complain	Management	Follow-up
1.	35/M	Loosening of maxillary teeth and exposed alveolar bone (Figs. 1 and 2) since 3 months	Surgical debridement (Figs. 3–5) and oral suspension of Posaconazole for 3–6 months	3 years
2.	25/F	Loosening of maxillary teeth and multiple draining sinuses from the maxillary alveolus since 2 months		2.5 years
3.	45/M	Loosening of maxillary teeth and nasal stuffiness since 3 months		2 years
4.	23/M	Loosening of maxillary teeth and pus discharge since 1.5 months		2 years
5.	60/F	Loosening of maxillary teeth 1 month		1.5 years
6.	35/M	Swelling on the right cheek since 3 months with loosening of teeth of right maxilla and pus discharge extraorally beneath the infraorbital rim since 1 month. CBCT depicted involvement of maxilla and zygomatic bone on the right side	Stage I: removal of necrotic maxillary bone followed by 3 months of Posaconazole therapy Stage II: removal of necrosed zygomatic bone and reconstruction	1.5 years

(Fig. 2). Tissue for histopathological and microbial cultural test revealed presence of mucor. All these patients were evaluated systemically for diabetes, hematological and renal disorders. In the absence of any immunocompromising disease an alternate therapy with surgical debridement and oral Posaconazole was planned. The maxillary buccal flap was raised; the necrosed grayish-yellow bone with the affected teeth was removed. The exposed sinus cavity was thoroughly irrigated with normal saline and all the loosened cyanosed soft tissue was removed. With the healthy bleeding bony margin, primary closure was achieved in all the cases (Figs. 3–5). In one of the six cases there was persistent draining fistula in the infraorbital region and the CT scan showed involvement of zygomatic bone, lateral orbital wall and infraorbital rim in addition to the maxillary dentoalveolar process. The surgical intervention was staged in two parts wherein the effected maxillary bone was removed intraorally followed by Posaconazole therapy that prevented further progress of the disease. After 3 months the remaining necrosed bone was removed and reconstruction was done with patient specific titanium implant in the second surgery. Histopathology and fungal culture showed no evidence of mucor in the necrotic bone after the second surgery.

An oral suspension of Posaconazole, 800 mg/24 h in two divided doses was prescribed for 12–16 weeks. After complete healing, the patients were rehabilitated with removable maxillary dentures. The patients were followed up for 1.5–3 years during which no radiographic assessment was done and the patients were

considered disease free by the absence of signs and symptoms. No recurrence of disease was observed in any of the six patients.

3. Discussion

An extensive review of literature by Mignogna et al. revealed 126 articles published between 1978 and 2009. Out of a total of 212 patients from 35 countries, India was the most effected with 94 (44.3%) patients, followed by USA and Australia with 42 (19.8%) and 12 (5.7%) patients respectively.³ Chakrabarti et al. have reported an increase in the frequency of mucormycosis in India from 13 cases per year in 1990–99 to 36 cases per year in 2000–04, and 50 cases per year in 2006–07, and the highest-risk group is patients with uncontrolled diabetes.^{12–14} The higher prevalence of mucormycosis in India can be related to climatic and socio-economic conditions and also to large diabetic population. The fungi has an affinity for blood vessels which they clog hampering the blood supply to the recipient bone that secondarily gets necrosed. Tissue sample for microbiology culture should always

Fig. 1. Atypical presentation of mucormycosis in an immunocompetent patient. Gingival recession, teeth mobility and pus discharge may misguide the clinician to make a diagnosis of aggressive periodontitis.

Fig. 2. Coronal CT scan showing the necrotic bone of hard palate and alveolar bone in maxilla.

Figs. 3–5. Aggressive debridement and sinus lavage with primary closure results in a healed defect.

include soft tissue as the necrosed bone seldom carries the microorganism. This often leads to difficulty in culturing it in the laboratory. Two out of 6 cases in the present series did not show the microorganism in the tissue sample initially and repeat biopsy and histopathological correlation led to a diagnosis of mucormycosis.

Our series of immunocompetent patients presented primarily with rhinomaxillary subtype of mucormycosis in which loosening of teeth with/without bone exposure was the most prominent feature. Dentists are the first to come across these patients due to the oro-dental presentation of the disease. Lack of awareness among them leads to mismanagement and delay in treatment and this further adds to the morbidity. All the six patients initially went to dentists or were referred to them for loosening of teeth and pus discharge, which they in their varied capacities performed dental treatment ranging from root canal therapy to periodontal surgery.

The universal treatment guidelines for mucormycosis consist of parenteral lipid formulation of Amphotericin B, radical surgical debridement, removal or control of underlying disease and improvement of the general health status.¹⁵ The administration of this drug needs hospitalization, central venous line and strict monitoring because of its known acute and chronic toxic side effects like nausea, vomiting, urticaria, rigors, fever, thrombophlebitis, etc. Its nephrotoxic nature requires monitoring of electrolytes, renal function, magnesium and phosphates on a regular basis during infusion. This has led to the search for an alternative drug with less toxic side effects. This case series highlights the efficacy of oral therapy with Posaconazole and raises the pertinent question that why this antifungal agent should not be the first line drug in mucormycosis?

Posaconazole is a relatively new broad-spectrum triazole with in vitro activity against various fungal pathogens like *Aspergillus*, *Candida*, *Mucor*, and *Fusarium* species. The formulation is a 40 mg/ml oral suspension containing polysorbate 80 as an emulsifying agent. It is administered at a dosage of 800 mg per day, in two or four divided doses. It has a long elimination half-life of 35 h, and its steady-state is reached in 7–10 days. Its absorption is promoted by nutritional supplements and high-fat meals and hence it should be administered with a full meal whenever possible, to ensure optimal absorption. There is no requirement of dose trituration even in cases of renal dysfunction as the kidneys have insignificant role in its excretion. None of our patients showed any side effect with this drug. Posaconazole has low risk of adverse effects, does not require parenteral administration and hence there is no need for hospitalization.¹⁶ It can also be used as a step down treatment after initial therapy with Amphotericin B. Two case series and more than 20 case reports of successful treatment with Posaconazole have been published and all conclude a significantly good and complete response.^{17,18}

It is also cost effective compared with Amphotericin B. A maximum dose of 3 g of lyophilized Amphotericin B in a month long treatment will cost the patient approximately

200,000–300,000 INR (3000 USD approx.) for the drugs, frequent biochemical tests and hospitalization at the rate of 6500–8000 INR/day (100 USD approx.). This does not include the cost of the family attendant, loss of work and emotional trauma. Compared to this, a 3-month treatment with oral Posaconazole will cost the patient approximately 180,000 INR (2700 USD approx.) at the rate of 2000 INR/day (30 USD approx.). There is no loss of work and the patient can stay at home during the therapy period. The comparison leaves no doubt that oral therapy with Posaconazole is less burdening to the patient both economically and emotionally.

We conclude that Posaconazole can be used for the treatment of rhinomaxillary mucormycosis in immunocompetent patients. Its efficacy against the fungus, minimal side effects and oral route makes it convenient both for the clinician and the patients though its efficacy against other forms of mucormycosis in immunocompromised patients needs to be investigated in future studies.

Conflicts of interest

The authors have none to declare.

References

- Petrikkos G, Skiada A, Lortholary O, Roilides E, Walsh TJ, Kontoyiannis DP. Epidemiology and clinical manifestations of mucormycosis. *Clin Infect Dis*. 2012;54(1):23–34.
- Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin Infect Dis*. 2005;41(5):634–653.
- Mignogna MD, Fortuna G, Leuci S, et al. Mucormycosis in immunocompetent patients: a case-series of patients with maxillary sinus involvement and a critical review of the literature. *Int J Infect Dis*. 2011;15(8):533–540.
- Varghese A, Thomas S. Orbital apex syndrome secondary to mucormycosis after a tooth extraction in an immunocompetent patient. *Ear Nose Throat J*. 2010;89:24–26.
- Goldstein EJC, Spellberg B, Walsh TJ, Kontoyiannis DP, Edwards Jr J, Ibrahim A. Recent advances in the management of mucormycosis: from bench to bedside. *Clin Infect Dis*. 2009;48(12):1743–1751.
- 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;46:1581–1582.
- Arikan S, Sancak B, Alp S, Hascelik G, McNicholas P. Comparative in vitro activities of Posaconazole, Voriconazole, Itraconazole, and Amphotericin B against *Aspergillus* and *Rhizopus*, and synergy testing for *Rhizopus*. *Med Mycol*. 2008;46:567–573.
- Burke D, Lal R, Finkel KW, Samuels J, Foringer JR. Acute amphotericin B overdose. *Ann Pharmacother*. 2006;40:2254–2259.
- Walker RW, Rosenblum MK. Amphotericin B associated leukoencephalopathy. *Neurology*. 1992;42:2005–2010.
- Roden MM, Nelson LD, Knudsen TA, Jarosinski PF, Starling JM, Shiflett SE. Triad of acute infusion-related reactions associated with liposomal amphotericin B: analysis of clinical and epidemiological characteristics. *Clin Infect Dis*. 2003;36:1213–1220.
- Fisher MA, Talbot GH, Maislin G, McKeon BP, Tynan KP, Strom BL. Risk factors for amphotericin B-associated nephrotoxicity. *Am J Med*. 1989;87:547–552.
- Chakrabarti A, Das A, Sharma A, et al. Ten years experience in zygomycosis at a tertiary care centre in India. *J Infect*. 2001;42:261–266.
- Chakrabarti A, Das A, Mandal J, et al. The rising trend of invasive zygomycosis in patients with uncontrolled diabetes mellitus. *Med Mycol*. 2006;44:335–342.
- Chakrabarti A, Chatterjee SS, Das A, et al. Invasive zygomycosis in India: experience in a tertiary care hospital. *Postgrad Med J*. 2009;85:573–581.

15. Cornely OA, Arian-Akdagli S, Dannaoui E, et al. ESCMID and ECMM Joint Clinical Guidelines for the Diagnosis and Management of Mucormycosis 2013. *Clin Microbiol Infect.* 2014;20(S3):5–26.
16. Ullmann AJ, Cornely OA, Burchardt A, et al. Pharmacokinetics, safety, and efficacy of Posaconazole in patients with persistent febrile neutropenia or refractory invasive fungal infection. *Antimicrob Agents Chemother.* 2006;50:658–666.
17. van Burik JA, Hare RS, Solomon HF, Corrado ML, Kontoyiannis DP. Posaconazole is effective as salvage therapy in zygomycosis: a retrospective summary of 91 cases. *Clin Infect Dis.* 2006;42:61–65.
18. Greenberg RN, Mullane K, van Burik JA, et al. Posaconazole as salvage therapy for zygomycosis. *Antimicrob Agents Chemother.* 2006;50:126–133.