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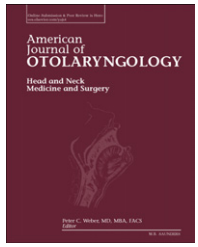

Successful Isavuconazole therapy in a patient with acute invasive fungal rhinosinusitis and acquired immune deficiency syndrome☆

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ABSTRACT

Objectives: To report a case of acute invasive Mucorales rhinosinusitis in a patient with acquired immune deficiency syndrome and diabetes mellitus. To provide a literature review on the role of Isavuconazole in the management of invasive Mucorales rhinosinusitis.

Methods: A literature review was conducted on August 9, 2015 using PubMed database. The keywords *isavuconazole* and *invasive fungal* rhinosinusitis were employed to identify original scientific manuscripts that describe the use of Isavuconazole in patients with invasive fungal rhinosinusitis or rhinocerebral mucormycosis.

Results: The initial search yielded 35 articles with only 1 article (case report) describing the clinical use of Isavuconazole in a patient with invasive Mucorales rhinosinusitis.

Conclusions: Acute invasive fungal rhinosinusitis is a rare, life-threatening infection with mortality rates reported to range from 30–83%. Successful treatment depends on early surgical debridement, systemic anti-fungal therapy, and correction of predisposing conditions. Isavuconazole (Cresemba), a newly approved antifungal, is safe and clinically effective in treating invasive mucormycosis. This important new therapy should be considered for patients with invasive Mucorales rhinosinusitis that is refractory or intolerant to Amphotericin B.

1. Case report

A 53 year-old male with acquired immune deficiency syndrome (AIDS) and poorly controlled diabetes mellitus (DM) presented with a 4-week history of progressive bilateral facial pain and diplopia. On initial examination there was no evidence of palatal or nasal mucosa necrosis, cranial palsies, or facial edema. His initial laboratory studies revealed a decreased white blood cell count (3.08×10^3 cells/μL), markedly decreased CD4 count (26 cells/μL) and markedly elevated HbA1c (12%). A non-contrast CT of his paranasal sinuses revealed bilateral pansinusitis with no evidence of bony erosion (see Fig. 1). Endoscopic sinus

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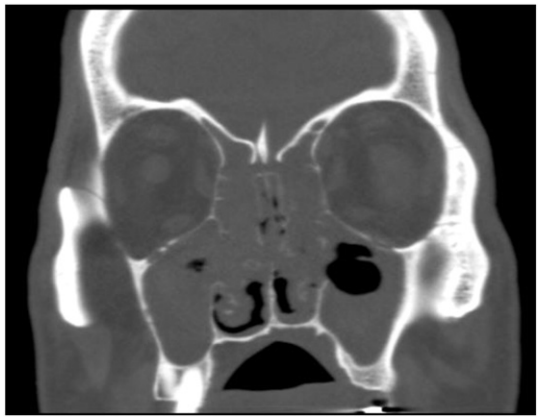

Fig. 1 – CT sinus without contrast from day 6 revealing pansinusitis without evidence of bony erosion.

examination revealed pansinus mucosal thickening and thick, yellow polypoid tissue. The paranasal sinuses were debrided and cultured. No evidence of necrosis or invasive fungal disease was noted endoscopically or on frozen sections. Initially, the concern for acute invasive fungal rhinosinusitis (AIFRS) was low based on clinical, surgical and histopathological examination.

On day 11, nasal sinus cultures identified *Rhizopus spp*. and repeat endoscopic examination revealed extensive necrosis involving the bilateral middle turbinates and the posterior nasal septum extending to floor of the nose. Histopathological examination revealed necrotic bone and mucosa with invasive fungal elements consistent with Mucorales. Necrotic areas were debrided endoscopically and combination antifungal therapy with IV Liposomal Amphotericin B (L-AMB) (10 mg/kg/day) and IV Micafungin was initiated for the treatment of acute invasive Mucorales rhinosinusitis. On days 13–17, his disease progressed to involve the bilateral ethmoid sinuses, bilateral sphenoid sinuses, right frontal sinus, bilateral maxillary sinuses, left medial maxilla and left inferior turbinate necessitating debridement of the involved sinuses, left medial maxillectomy, left inferior turbinectomy, and left sphenopalatine artery ligation.

Clinically, the patient remained stable throughout his admission and his bilateral facial pain and diplopia resolved. On day 25, clinical, surgical, histopathological, and radiographic examination did not reveal evidence of AIFRS. Consequently, he was discharged from the hospital on long-term L-AMB and Micafungin.

On day 65, he presented with recurrent invasive fungal rhinosinusitis. Surgical, radiographic, and histopathological examination demonstrated involvement of the anterior skull base and bilateral pterygopalatine fossae extending to the inferior orbital fissures (see Fig. 2). In total, 12 serial endoscopic debridements were required to resect the diseased tissues. Due to the refractory nature of his infection and the development of renal insufficiency (serum potassium 2.2 mmol/L; serum creatinine 2.35 mg/dL) secondary to L-AMB, a newly approved antifungal drug, Isavuconazole (Cresemba), was recommended as an alternative. On day 76, IV Isavuconazole was initiated (loading dose 372 mg every 8 hours for 48 hours; maintenance dose 372 mg daily) for the treatment of L-AMB refractory/intolerant invasive Mucorales rhinosinusitis.

At his most recent follow-up (day 94), the patient has significantly improved. Surgical and histopathological examinations revealed trace areas of necrosis involving the bilateral pterygopalatine fossae without evidence of fungal elements (see Fig. 3). Clinically, he does not report any significant symptoms or long-term sequelae. Isavuconazole was well tolerated without adverse effects except for elevated liver enzymes (alkaline phosphatase 1021 IU/L, AST 47 IU/L, ALT 48 IU/L). He continues to receive ongoing therapy with IV Isavuconazole and close observation with weekly endoscopic and histopathological examinations.

2. Discussion

Acute invasive fungal rhinosinusitis (AIFRS) is a rare but frequently fatal infection that usually affects patients with poorly controlled DM and/or immunosuppression. AIFRS is characterized by fungal invasion of the paranasal sinuses and nasal cavity with frequent extension to adjacent structures, including the palate, orbit, and brain. Recognition of evolving AIFRS requires a high index of suspicion because early symptoms may mimic acute sinusitis (e.g. sinus pain, headache, congestion). The disease is heralded by rapid progression with symptoms of facial edema, vision changes, and cranial nerve palsies associated with evidence of pale ischemia, purple black crusting, or frank necrosis. Concurrent surgical, clinical, and radiologic examination may help establish the diagnosis but definitive diagnosis requires histopathological confirmation of invasive fungal elements [1–5].

The organisms primarily responsible for AIFRS include species from the genus *Aspergillus* and the order Mucorales, which includes *Mucor spp*. and *Rhizopus spp*. These saprophytic fungi are ubiquitous in the environment, but may become pathogenic in patients with impaired neutrophil activity and/or hyperglycemia. Normally, these fungi are cleared by polymorphonuclear phagocytes and possess an active ketone reductase system allowing them to thrive in acidic, glucose rich environments [1–3]. Thus, AIFRS primarily affects immunocompromised and/or DM patients, and reversal of these predisposing conditions is essential for disease clearance [1–4].

Despite aggressive multimodal therapy, the prognosis of AIFRS remains grim with short-term mortality rates reported to range from 30–83% [1–4,6–8]. Successful treatment depends on a timely diagnosis, aggressive surgical debridement, high dose systemic anti-fungal therapy, and management of predisposing risk factors.

Amphotericin B is the drug of choice for the treatment of invasive mucormycosis [1–4,6–9]. Unfortunately, high doses of conventional Amphotericin B are poorly tolerated and significant nephrotoxicity usually develops if administered for more than a few days. Lipid formulations of Amphotericin B are associated with reduced rates of nephrotoxicity; however, significant rates of nephrotoxicity can develop at high doses [6–9]. Additionally, Mucorales are highly resistant to most antifungals and may demonstrate resistance to Amphotericin B [4,7,9]. Thus, alternative antifungals are essential for patients who cannot tolerate Amphotericin B and for patients with refractory invasive Mucorales rhinosinusitis.