Successful Treatment of *Aspergillus* Sinusitis with Oral Voriconazole: A Case Report

Shih-Jie Jhuo, Wei-Sheng Wang¹, and Jen-Yuan Kuo

Division of Cardiovascular Diseases,
¹Division of Infectious Diseases,
Department of Medicine,
Mackay Memorial Hospital, Taipei, Taiwan, ROC

Abstract

*Aspergillus* sinusitis is an infection that can cause high mortality without appropriate treatment. The infection is not only found in immunocompromised patients, but also in immunocompetent patients. Management approaches to *Aspergillus* sinusitis include surgical debridement and intravenous or oral antifungal agents, including traditional intravenous amphotericin B. Here we describe a case of *Aspergillus* sinusitis with maxillary and orbital bony destruction. After surgical debridement, oral voriconazole was given to this patient due to the fact that he had poor renal function. After he had been administered with voriconazole 400 mg/day for 33 days, the infection was resolved completely. (J Intern Med Taiwan 2011; 22: 63-68)

Key Words: Aspergillosis, Sinusitis, Voriconazole

Introduction

Invasive aspergillosis is mostly found in immunocompromised patients¹-³ and is generally fatal without adequate treatment⁴. It is also frequently found in patients with uncontrolled diabetes mellitus (DM) who are in an immunocompromised state⁴,⁵,⁶. Mucormycosis is generally thought to be more prevalent than aspergillosis in diabetic patients. However, invasive aspergillosis is more prevalent than mucormycosis when the patient is suffering from paranasal sinusitis and the mortality rate ranges between 35% and 66%⁵,⁷. Clinically, it is difficult to distinguish mucormycosis from aspergillosis without histological evidence²,³. The most common symptoms of fungal sinusitis are headache, proptosis, rhinorrhea and ophthalmoplegia. Invasive aspergillosis can start in the paranasal sinus and spread to the orbital or skull base with bone destruction and/or vessel infiltration⁸. The primary treatment for aspergillosis includes surgical debridement and anti-fungal therapy. Amphotericin B is the first-line anti-fungal therapy, but this drug has significant renal and hepatic toxicity. Voriconazole is recommended as the first-line antifungal agent for invasive aspergil-
losis. In some studies, voriconazole or itraconazole has shown good efficacy and fewer adverse effects than amphotericin B. We present a patient with Aspergillus sinusitis who was treated successfully with oral voriconazole.

Case Report

The patient was a 71-year-old man who had type 2 DM with nephropathy, ischemic heart disease and atrial fibrillation. He presented with progressive headache affecting the left frontal, temporal and periorbital area for two months. Easy tearing and mild slurred speech were also found. He denied consciousness loss, blurred vision, hearing loss, facial palsy and limb weakness. He also denied trauma history. He had the history of soil and chicken stool contact. He visited the Neurology Department and a physical examination showed paresthesia in the cranial nerve V1 and V2 region. Erythematous change and swelling of the left lower eyelid were also noted. Initial laboratory examination showed anemia (Hb: 8.8 g/dL). No leucocytosis was noted (WBC: 4,900/µl, Neutrophil: 79%). Biochemistry showed hyperglycemia (186 mg/dL), an elevated CRP (3.46 mg/dL) and impaired renal function (BUN/Cr: 38/3.8 mg/dL). A brain computed tomography showed suspected cellulitis with a superimposed fungal infection with bony destruction of the left maxillary sinus and the left orbital cavity (Figure 1-a). Left sphenoid sinusitis was also suspected. A brain magnetic resonance imaging revealed mucosal thickening with calcification involving the left maxillary sinus and left posterior ethmoid sinus (Figure 1-b). Mucormycosis of the left maxillary sinus with orbital cavity invasion was highly suspected at first. This patient has been suspected of having fungal sinusitis two to three years earlier based on nasal obstruction that had lasted for months but he did not receive any treatment. Based on the insidious clinical course and the past history of suspected fungal sinusitis, aspergillosis was also considered as an alternative to mucormycosis. An otolaryngologist was consulted and debridement by functional endoscopic sinus surgery (FESS) was arranged. The

Figure 1-a

Figure 1-b

Fig.1 a. A CT image of transverse axial view of Aspergillus infection in left maxillary sinus (arrow) with bony destruction and left orbital cavity involvement. b. A MRI image of sagittal view of Aspergillus infection involving left maxillary sinus with invasion to medial inferior aspect of left orbital cavity (arrow).
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FESS showed much black dirty material with some calcified pus formation. Biopsy and fungal culture were carried out at the same time. The pathological report showed the presence of a fungus with septate dichotomous branching and $45^\circ$ angles to the branches (Figure 2). Aspergillosis was diagnosed based on the pathological findings. No invasive hyphae were found within the nasal mucosal tissue. Due to the patient’s renal function impairment, his family refused treatment with intravenous amphotericin B. Therefore, oral voriconazole 200 mg bid was administered as a monotherapy. After treatment with voriconazole for 10 days, a fever reaching $38^\circ C$ was noted. A chest X-ray showed bilateral lower lobe consolidation, and nosocomial pneumonia was considered. He was treated with intravenous piperacillin/tazobactam for 13 days, which was followed by oral moxifloxacin. The blood culture showed no growth after 5 days. His fever and pneumonia subsided after treatment. To control his blood glucose level, insulin glargine 30 U per day was initiated to replace the oral hypoglycemic agents. After he had been prescribed voriconazole 200mg bid for 33 days, he was discharged free of symptoms and signs. After follow-up at out patient department for 1 month and evaluation by an Ear, Nose and Throat specialist, no residual lesion was found. There were no sequelae over the 6 months after oral voriconazole was withdrawn.

**Discussion**

*Aspergillus* sinusitis usually occurs in diabetic and immunocompromised patients. Invasive aspergillosis can cause high morbidity and mortality. Most patients who develop invasive aspergillosis are likely to have had prolonged granulocytopenia, graft-versus-host disease, immunosuppressive therapy, corticosteroids usage, or prolonged impairment of the host defenses\(^9,10\). However, rare cases have been reported in immunocompetent patients\(^1,3\). The differential diagnosis of invasive fungal sinusitis in type 2 DM patients includes mucormycosis and *Aspergillus* infection. Usually, we assume that the incidence of mucormycosis is higher than that of *Aspergillus* infection in diabetic patients. However, in some reports, *Aspergillus* infection is more prevalent than mucormycosis among diabetic patients with paranasal sinusitis\(^5\). In Taiwan, it is also one of the most common zygomycosis species that cause fungal sinusitis\(^11\). The sphenoid and ethmoid sinuses are the most frequently involved\(^11,12\).

Most symptoms of *Aspergillus* infection are non-specific and include nasal blockade, followed by proptosis and rhinorrhea\(^8,11\). The orbital manifestations are non-axial proptosis, telecanthus, ophthalmoplegia and bulging of the medial canthus\(^1,11\). Headache, seizures, mental deterioration, cavernous sinus syndrome and cranial nerve deficits are also found\(^8,12\). Occlusion of the central retinal artery and compression and/or involvement of the optic nerve can cause visual loss. More than 700 *Aspergillus* species have been identified. *Aspergillus fumigatus* (80%-90%) is the cause of most invasive aspergillosis. *Aspergillus flavus* (5%-10%), *Aspergillus niger* (1%-5%), and *Aspergillus terreus* (1%) are found less frequently\(^8\). Traditionally,
the definitive diagnosis is verified by histological examination. Compared to mucormycosis, which involves non-septate hyphae and right-angle branching, aspergillosis shows septate hyphae with $45^\circ$ branches. However, other hyalohyphomycetes, for example, Fusarium and Pseudallescheria boydii, have similar histological characteristics to Aspergillus and other more complex methods, such as immunohistochemical study and polymerase chain reaction, are needed to obtain a specific evaluation.

Sinonasal mycotic disease can be classified to (1) acute fulminative (vascular invasion, thrombotic ischemia), (2) chronic invasive, (3) non-invasive and (4) allergic. The allergic type is characterized by eosinophilia, elevated IgE and a positive reaction with an anti-Aspergillus precipitin test and immediate hypersensitivity test to Aspergillus. Allergic mucin with Charcot-Leyden crystal can be found on histological examination. In the invasive group (chronic invasive and fulminantive types), hyphae can invade the sinus mucosa, bone, orbital tissue, and even the intracranium. By the contrast, the non-invasive type usually develops into the invasive type in certain immunosuppressive states. According to a study in Taiwan, chronic non-invasive aspergillosis and acute invasive sinusitis are the two most common types of fungal sinusitis.

The treatments used for aspergillosis included surgical debridement together with intensive antifungal drugs. Orbital extension has to be considered in individual cases, especially in patient with ophthalmoplegia and blindness. Compared with mucormycosis, aspergillosis has a better prognosis. Amphotericin B is the one of the commonly available anti-fungal treatments for aspergillosis and has an efficacy rate of about 40% to 60% in invasive aspergillosis. However, amphotericin B has considerable renal and hepatic toxicity. Anemia, fever, and electrolyte abnormalities have also been noted. A study of 108 patients where amphotericin B was used to treat invasive fungal sinusitis revealed nephrotoxicity development as a significant predictor of mortality and increased hospital stay. In another study from Taiwan, isolates of A. flavus and A. fumigatus with a reduced susceptibility towards amphotericin B have been found. Among the four species tested, A. flavus was the least susceptible to amphotericin B.

In our case, due to poor renal function, we prescribed voriconazole alone to control the Aspergillus infection. Voriconazole has the advantage of better tolerance, increased efficacy, and significantly less toxicity when compared with amphotericin B. Voriconazole is hepatically metabolized and therefore can be given as an oral pill. It also shows less nephrotoxicity and there is better compliance than with amphotericin B in clinical practice. In a study of 277 patients with definite or probable aspergillosis, 144 patients received voriconazole treatment alone and 133 patients receive amphotericin B treatment. The success rate for the patients in the voriconazole group was 52.8% (complete response in 20.8% of cases and partial responses in 31.9% of cases) and 31.6% in the amphotericin B over twelve weeks. The survival rate at 12 weeks was 70.8% and 57.9%, respectively. As a result, voriconazole is recommended as the first-line treatment for invasive aspergillosis. Visual disturbances and hepatic abnormality are more common in patients using prolonged voriconazole. The most frequent descriptions of such disturbances are blurred vision, altered visual perception, altered color perception, and photophobia. All these visual events were transient and resolved without intervention. In some studies, a combination therapy of voriconazole and caspofungin has been shown to have a synergic effect and no obvious interaction between caspofungin and voriconazole was found.
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than those who received voriconazole only\(^\text{18}\). Thus voriconazole was a better option of treatment with the present patient because of his severe renal function impairment.

In conclusion, aspergillosis is a rare filamentous fungal infection and occurs mostly in immunocompromised patients. The mainstay of aspergillosis treatment includes surgical debridement and anti-fungal therapy. Traditionally, amphotericin B is the first-line anti-fungal agent used for such treatment, but there is the possibility of significant adverse effects including renal and hepatic toxicity. In our case, anti-fungal therapy with oral voriconazole alone showed good efficacy and was well tolerated. Based on the literature and our experience, voriconazole ought to play a more important role in the treatment of invasive aspergillosis than at present and perhaps should replace amphotericin B as the treatment of choice.

**References**

口服性 Voriconazole 治療鞠菌性鼻竇炎之成功案例：
病例報告

卓士傑 王威勝 1 郭任遠
台北馬偕醫院 內科部 感染科 1 心臟內科

摘要

鞠菌性鼻竇炎 (Apergillus sinusitis) 若無適當的治療，能造成極高的致死率。此疾病不僅
能在免疫力受損的病人上發現，有時也能在免疫力健全的病人上發現。臨床上，治療鞠菌性
鼻竇炎的方法包括外科手術及給予以靜脈注射或是口服抗黴菌抗生素，包括了傳統上靜脈注
射 amphotericin B。在此病例報告中，我們將敘述一位病人感染鞠菌性鼻竇炎並造成上頜骨及
周邊眼框骨 (maxillary and orbital bone) 的破壞。經外科手術治療後，因病人腎臟功能不佳而
給予口服 voriconazole 治療成功的案例。在 33 天給予 voriconazole 400 mg/day 治療後，病人
的感染症狀完全改善，並無明顯的後遺症發生。