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Case Report

Successful Treatment of Two Cases of Invasive *Aspergillus* Sinusitis With Voriconazole

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Abstract

Aspergillosis is a spectrum of diseases caused by *Aspergillus* spp., which is a widespread fungus that produces microscopic spores. Immunocompetent people may breathe in numerous *Aspergillus* spores every day, yet experience no symptoms. Invasive *Aspergillus* sinusitis is relatively rare. There is limited information about the use of voriconazole for the treatment of invasive *Aspergillus* sinusitis. Here, we present two cases of invasive *Aspergillus* sinusitis in elderly female patients with diabetes mellitus. Both patients fully recovered after treatment using surgical debridement and an antifungal regimen that included voriconazole. (*Tzu Chi Med J* 2010; 22(2):106–110)

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1. Introduction

Aspergillosis is a spectrum of diseases caused by *Aspergillus* spp., a ubiquitous spore-forming saprophytic thermotolerant fungus. *Aspergillus* spp. is commonly found in soil, dust, plants, and decaying vegetable matter. It releases microscopic airborne spores that can easily enter the alveoli of the lung.

Invasive aspergillosis is the most common fungal infection worldwide and often occurs in immunocompromised patients (1,2). Common risk factors for aspergillosis are hemopoietic stem cell transplantation, solid organ transplantation, intensive chemotherapy, neutropenia, pulmonary disease, liver cirrhosis, and corticosteroid therapy (1,2). The lung is the most commonly affected organ, followed by the liver, spleen, heart, bones, and central nervous system (1,2).

Invasive *Aspergillus* sinusitis is relatively rare (3,4). This condition is treated using surgery and antifungal agents (3,5–7). Previously, amphotericin B was commonly administered for invasive aspergillosis, but this drug can cause severe adverse effects (8,9). In addition, amphotericin treatment of invasive aspergillosis requires intravenous (i.v.) administration, so treatment typically requires prolonged hospitalization.

Voriconazole is a newly-developed antifungal triazole medication that is available in oral and i.v. forms. The drug appears to be effective in the treatment of patients with invasive aspergillosis (10,11), but there is limited knowledge about its efficacy in the treatment of invasive *Aspergillus* sinusitis. Here, we present

two patients with invasive *Aspergillus* sinusitis who were successfully treated using voriconazole.

2. Case reports

2.1. Case 1

A 69-year-old woman who had been diagnosed with diabetes mellitus and hypertension for several years presented with complaints of intermittent headaches for 3 months prior to this admission. The headaches progressed and she did not respond to analgesic medications. Five days prior to this admission, the vision of her right eye became blurred. Physical examination revealed impaired right visual acuity and right abducens nerve palsy.

A peripheral hemogram indicated a leukocyte count of $9.8\times10^3/\mu L$ with 80.6% segment form, hemoglobin of 11.5 g/dL, mean corpuscular volume of 85.6 fL and platelet count of $217\times10^3/\mu L$. All electrolyte levels were within the reference ranges. Serum urea nitrogen was 25 mg/dL, creatine was 1.2 mg/dL, serum aspartate aminotransferase was 37 IU/L, alanine aminotransferase was 54 IU/L, and C-reactive protein was 0.52 mg/dL. Brain magnetic resonance imaging (MRI) with and without gadolinium-labeled diethylenetriamine indicated an encapsulated heterogeneous cystic lesion in the sphenoid sinus, with invasion of the bone and cranial nerve (Fig. 1).

We performed transnasal endoscopic removal of the mass on the 4th day of hospitalization, and noted the presence of soft and friable necrotic tissue within the sphenoid sinus. Tissue culture yielded *Staphylococcus aureus* susceptible to oxacillin. Histopathology indicated the presence of many uniform hyphae with frequent septation and dichotomous branching, compatible with *Aspergillus* spp. (Fig. 1).

We administered i.v. voriconazole and oxacillin on day 4. The voriconazole regimen consisted of a loading dose, 6 mg/kg every 12 hours for two doses, followed by a maintenance dose, 4 mg/kg every 12 hours.

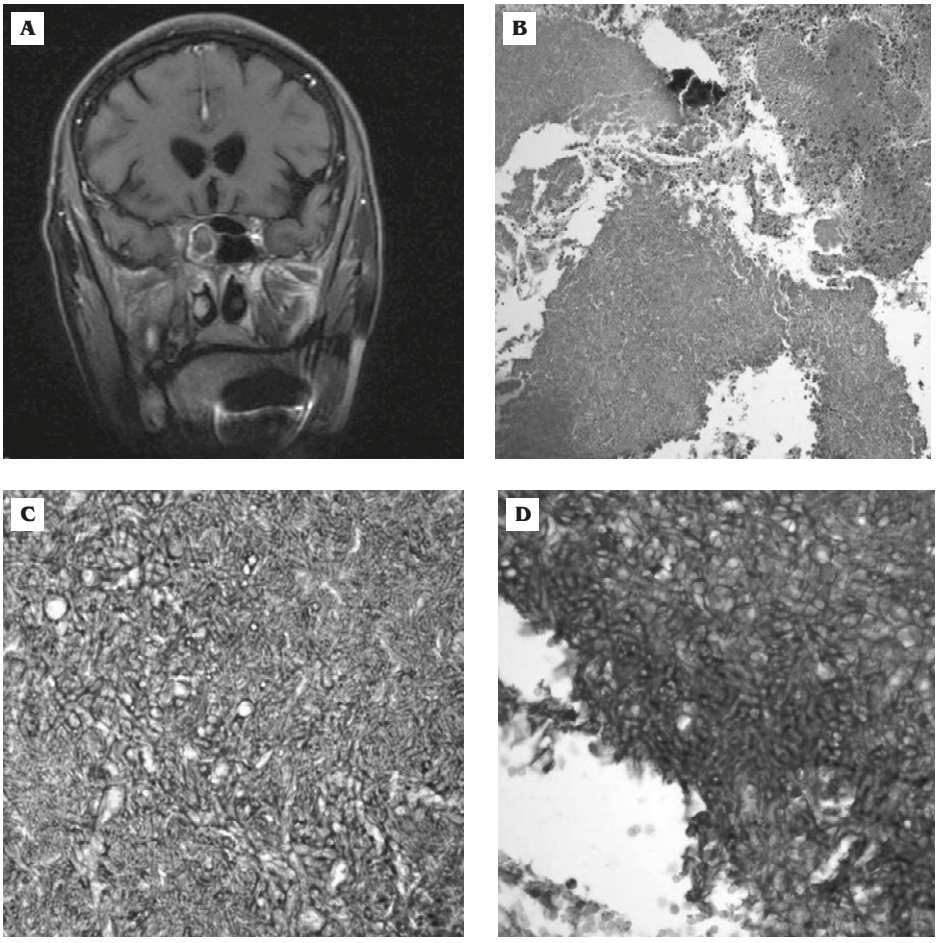

Fig. 1 — (A) Brain magnetic resonance imaging shows an encapsulated heterogeneous cystic lesion in the sphenoid sinus with bone invasion. (B) Histological examination with hematoxylin and eosin demonstrates hemorrhaging necrotizing tissues (100×). Many uniform hyphae with frequent septation and dichotomous branching, compatible with *Aspergillus* spp., are seen with: (C) hematoxylin and eosin (400×); and (D) periodic acid-Schiff (400×).

Her symptoms became milder but fever occurred on day 24. Serum immunoglobin M against *Leptospira* spp. (LeptoTek Lateral Flow; bioMérieux BV, Boxtel, The Netherlands) was weekly positive. Blood culture yielded *Stenotrophomonas maltophilia* and *Comamonas acidovorans*. We removed the central line and changed the antibiotics to 3 MU i.v. penicillin G every 4 hours and 800/160 mg i.v. sulfamethoxazole/trimethoprim every 8 hours. After a 14-day course of penicillin G and sulfamethoxazole/trimethoprim and a 60-day course of i.v. voriconazole, her symptoms subsided. We changed the voriconazole to the 200 mg oral form, administered every 12 hours for 35 days. She was free of symptoms at the 8-month follow-up examination.

2.2. Case 2

A 75-year-old woman who had a history of hypertension and diabetes mellitus presented with left lower eyelid swelling that she had experienced for a week prior to this admission. The swelling progressed and the patient complained of local heat and tenderness. Physical examination indicated a tender, reddish swelling of her left eyelid.

A peripheral hemogram indicated a leukocyte count of $25.5 \times 10^3/\mu L$ with 82% segment and 1% band form, hemoglobin level of 12.8 g/dL, mean corpuscular volume of 92.5 fL, and platelet count of $333 \times 10^3/\mu L$. Serum sodium was 130 mmol/L, potassium was 3.6 mmol/L, urea nitrogen was 21 mg/dL, creatine was 0.5 mg/dL, aspartate aminotransferase was 20 IU/L, alanine aminotransferase was 26 IU/L, and C-reactive protein was 0.52 mg/dL. Computed tomography indicated the presence of an expansile soft tissue mass in the left maxillary, frontal, and ethmoid sinuses (Fig. 2).

We initially administered i.v. penicillin and cefepime. These were not effective, so debridement was performed on day 3. Histopathology indicated the presence of many uniform hyphae with frequent septation and dichotomous branching as well as invasion of

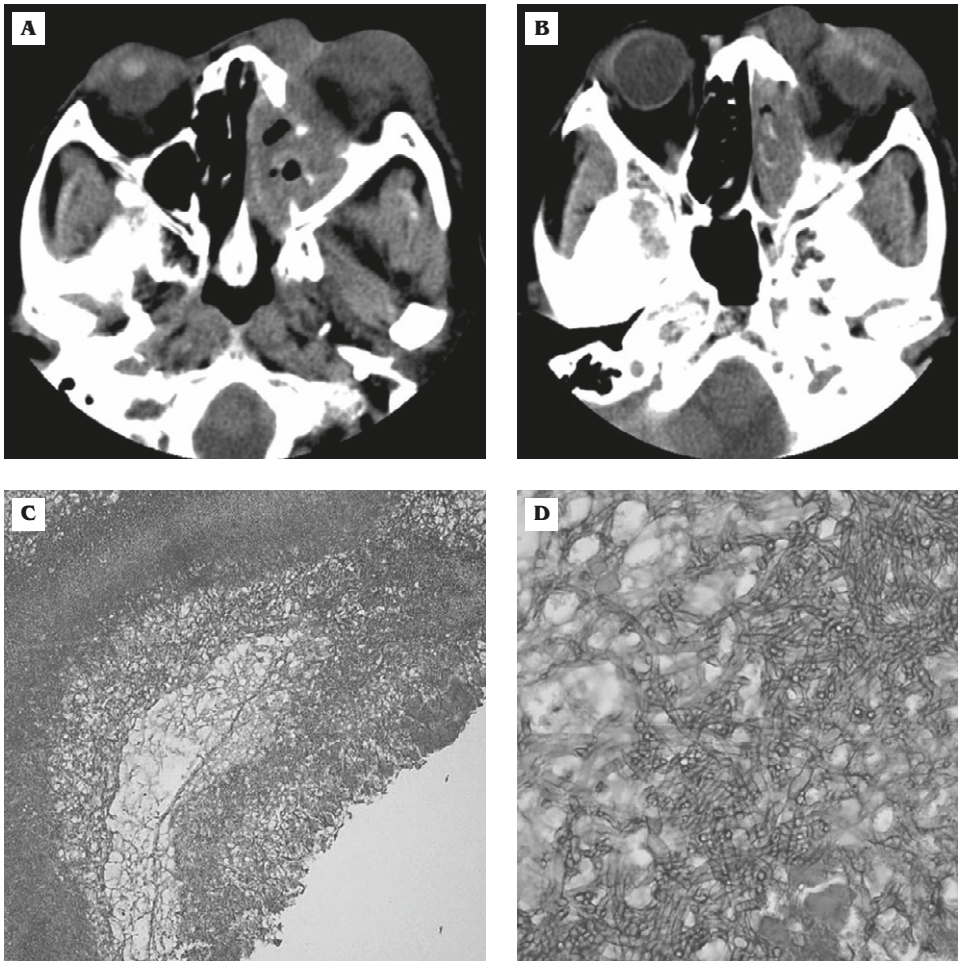

Fig. 2 — Computed tomography shows an expansile soft tissue mass in the left: (A) ethmoid sinuses; and (B) sphenoid sinuses. Histological examination with hematoxylin and eosin demonstrates: (C) necrotizing tissues at low magnification of 100×; and (D) many uniform hyphae compatible with invasive aspergillosis at high magnification of 400×.

tissue, which was compatible with invasive aspergillosis (Fig. 2). Pus and tissue culture yielded *Klebsiella pneumoniae*.

We administered 5 mg/kg i.v. liposomal amphotericin B per day after the operation and changed it to i.v. voriconazole on day 6. The voriconazole regimen consisted of a loading dose, 6 mg/kg every 12 hours for two doses, followed by a maintenance dose, 4 mg/kg every 12 hours. Serum immunoglobin M against *Leptospira* spp. (LeptoTek Lateral Flow; bioMérieux BV) was weakly positive. The patient's low-grade fever persisted, so we performed a second debridement on day 13, after which her fever subsided. Sinoscopy, performed on day 21, indicated clarity of the left maxillary and frontal sinuses. We discontinued i.v. penicillin and cefepime on day 21, and discharged the patient on day 25, at which time we prescribed 200 mg oral voriconazole every 12 hours for 28 days. The patient was free of symptoms at the 18-month follow-up examination.

3. Discussion

Aspergillus is very common in the daily environment and is the leading cause of fungal sinusitis [12]. *A. fumigatus* is the most common species involved, followed by *A. flavus*, *A. niger* and *A. terreus* [13–15]. Most immunocompetent patients who experience sinus colonization by *Aspergillus* spp. remain symptom-free. Invasive aspergillosis typically occurs in immunocompromised patients, such as those with hematological malignancy, neutropenia, steroid exposure, diabetes mellitus, and liver disease [1,2]. The diagnosis of *Aspergillus* sinusitis is often delayed, particularly in immunocompetent patients. The most common symptoms of aspergillosis are headaches, proptosis, nasal obstruction, decreased visual acuity, retro-orbital pain, epistaxis, diplopia, and sinus or facial tenderness [3]. Aspergillosis should be suspected in patients with refractory or recurrent sinusitis [5]. In the two cases described here, one patient presented with right abducens nerve palsy and the other with swelling of the left lower eyelid. Although both patients had diabetes mellitus, their otherwise normal immunological statuses did not lead physicians to initially suspect aspergillosis.

The typical appearance of fungal sinusitis on computed tomography is a central radio-opaque lesion, which is possibly related to calcium phosphate deposition in necrotic areas [12,16,17]. The decreased signal intensity on T1-weighted MRI and much decreased signal intensity on T2-weighted MRI seem to be characteristic of mycetomas [18]. Positive culture results from sterile sites consistent with infection are needed but the urine and mucous membranes should be excluded [19]. Definite diagnosis of invasive *Aspergillus* sinusitis requires positive histopathological or cytopathological examination results. In both of our cases, evidence of hyphae and associated tissue damage in the biopsy specimens were consistent with the diagnosis of invasive *Aspergillus* sinusitis.

Standard treatment of invasive aspergillosis sinusitis includes surgical debridement and administration of antifungal agents [3,5]. Amphotericin B is commonly administered for the treatment of invasive aspergillosis [20–22], but may be associated with many adverse effects [8,9]. In addition, amphotericin is only available in the i.v. form, so prolonged hospitalization may be required. Voriconazole, a cytochrome P450-dependent 14-α-sterol demethylase inhibitor, has excellent activity against *Aspergillus* spp. *in vitro* and the oral bioavailability is greater than 90%. After the i.v. loading regimen, patients can be given oral voriconazole, with no need for hospitalization [23]. A previous randomized and unblinded trial that compared voriconazole and amphotericin B for the treatment of aspergillosis showed that voriconazole was associated with better responses and survival rates, as well as fewer side effects [24]. The most common adverse effects of voriconazole are transient visual disturbance, abnormal liver enzymes, photosensitivity and skin rashes, but these typically resolve when the drug is discontinued. We treated both of our patients with surgical debridement and adjuvant antifungal agents. In one patient, we administered i.v. voriconazole initially; in the other patient, we first administered liposomal amphotericin B, and then changed to voriconazole. Both patients tolerated the voriconazole well and eventually recovered from the invasive *Aspergillus* sinusitis.

Both of our patients tested positive for serum immunoglobulin M against *Leptospira* spp. We are unsure whether these positive responses are meaningful, or are merely false-positive responses due to the lack of result on the microscopic agglutination tests. Invasive aspergillosis was reported in the autopsies of three patients with leptospirosis [25]. Another researcher identified invasive pulmonary and cerebral aspergillosis in a patient with leptospirosis [26]. None of the patients were in severe immunocompromised states. The immune statuses of the two patients presented here, who both tested positive for *Leptospira*, were not bad enough to suggest invasive aspergillosis. However, leptospirosis can lead to vasculitis and consumptive coagulopathy [27], thus possibly increasing the permeability of vessels and allowing colonized *Aspergillus* spp. to invade nearby tissues. Such a mechanism may explain why invasive aspergillosis is occasionally found in immunocompetent patients [28–30].

In conclusion, we have presented two rare cases of invasive *Aspergillus* sinusitis. *Aspergillus* spp. invaded the sphenoidal sinus of one patient and multiple

sinuses in the other patient. We successfully treated both patients using surgical debridement and antifungal regimens that included voriconazole. Both patients tested positive for immunoglobulins against *Leptospira* spp. Thus, we suggest that future clinical studies examine the relationship between invasive aspergillosis and leptospirosis.

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