New treatment for invasive fungal sinusitis: Three cases of chronic invasive fungal sinusitis treated with surgery and voriconazole

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Abstract

Invasive fungal sinusitis is a relatively rare disease and can be divided into acute fulminant, chronic, and granulomatous invasive fungal sinusitis. The conventional treatment is radical surgery combined with systemic amphotericin B administration, but the poor prognosis and unestablished treatment options require a better therapeutic strategy. We report three cases of chronic invasive fungal sinusitis successfully treated with a combination of surgery and voriconazole, a new antifungal agent, with good responses in all patients. Voriconazole administration could form the basis for a new standard treatment for invasive fungal sinusitis.

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1. Introduction

Fungal sinusitis often occurs as the non-invasive type and only simple removal of the fungus is required for full recovery. In contrast, invasive fungal sinusitis is rare and requires systemic administration of antifungal agent plus extended surgical removal. Invasive fungal sinusitis is defined as fungal sinusitis with mucosal infiltration of mycotic organisms [1] and can be classified into three categories, granulomatous, acute fulminant, and chronic invasive, depending on the histological features [2]. Both non-invasive and invasive fungal sinusitis are usually the result of Aspergillus species infection [3]. Acute fulminant invasive fungal sinusitis usually occurs in an immunocompromised host, but any person can suffer chronic invasive fungal sinusitis [4,5]. The gold standard for treatment has been wide surgical debridement, intravenous administration of antifungal agents such as amphotericin B, and correction of the underlying immunocompromised state [4]. However, the prognosis remains poor, partly because the strong side effects of amphotericin B, which are sometimes critical and can hinder long time administration.

New antifungal agents have recently been developed with weaker side effects and higher efficacy [6]. A large randomized open multicenter trial comparing amphotericin B and voriconazole for the treatment of invasive aspergillosis showed significant better outcome and fewer adverse events with voriconazole group [7]. However, no standard treatment option with the new antifungal agents has yet been established for chronic invasive fungal sinusitis.

We describe three cases of chronic invasive fungal sinusitis who were treated with the combination of surgery and extended administration of voriconazole, resulting in good clinical outcome in all three patients. Voriconazole may be the first choice antifungal agent to treat chronic invasive fungal sinusitis and might improve the conventional prognosis.

2. Case reports

2.1. Case 1

An 82-year-old man with a history of myocardial infarction treated with percutaneous transluminal coronary
angioplasty, chronic obstructive pulmonary disease, and hepatitis C virus infection was referred to our hospital in March 2008 for right maxillary lesion confirmed with computed tomography (CT), manifesting as right cheek pain.

On admission, coronal CT demonstrated extensive disease in the right maxillary sinus. The bone of the orbital floor was absorbed and the lesion had intruded into the orbit. Axial CT demonstrated widening of the natural ostium of the right maxillary sinus (Fig. 1a and b). Coronal T1-weighted magnetic resonance (MR) imaging with gadolinium showed hypertrophic maxillary mucosa and orbital infiltration. Axial T1-weighted MR imaging with gadolinium showed an expansive lesion in the maxillary sinus (Fig. 1c and d). Malignant disease was suspected, so biopsy was performed through the canine fossa approach. Histological examination confirmed tissue invasion by narrow septate hyphae, with branching at 45° consistent with Aspergillus species, and infiltration of chronic inflammatory cells, but no eosinophils or granuloma were observed (Fig. 2a). Systemic micafungin (MCFG) infusion (50 mg/day) was started 11 days after the biopsy. The Caldwell-Luc procedure was performed with removal of the maxillary mucosa. The mucosa was thick and hyperemic, as typically observed with acute maxillary sinusitis. No sign of necrosis was observed. The natural ostium of the maxillary sinus was widened. The lesion in the orbit was preserved. The pain in the right cheek persisted so the antifungal agent was changed to voriconazole (loading dose 600 mg/day on the first day and 400 mg/day thereafter). Cheek pain remitted in a few weeks. Two months after the start of voriconazole administration, the dose was reduced to 300 mg/day because of mild liver and kidney dysfunction. Liver and kidney function recovered without additional therapy.

Follow-up MR imaging performed in June, July, and November 2008 showed that lesion in the orbit had been significantly diminished (Fig. 2b–d). Voriconazole administration has been continued for 8 months without recurrence.

2.2. Case 2

A 73-year-old man with a history of benign prostatic hypertrophy was referred to our hospital in May 2008 with a left sphenoid lesion confirmed with CT.

On admission, CT showed opacity of the left sphenoid sinus with bone thickening (Fig. 3a and b). Axial T1-weighted MR imaging demonstrated opacification of the left sphenoid sinus with heterogeneous intensity. There was no expansion to the surrounding tissue (Fig. 3c). Axial T2-weighted MR imaging demonstrated opacification of the left sphenoid sinus with signal void (Fig. 3d). The lesion limited to within the sphenoid sinus indicated the differential diagnosis of chronic sinusitis and fungal sinusitis. The signal void in the sphenoid was compatible with one of the characteristics of fungus ball. Functional endoscopic sinus
surgery was performed with septoplasty. The sphenoid sinus was filled with pus and blackish material. The mucosa of the sphenoid was slightly edematous. Simple removal of the fungus ball was performed without radical extraction of the sphenoid mucosa. Histological examination of the sphenoid mucosa confirmed mucosal Aspergillus invasion. Systemic voriconazole administration (loading dose 600 mg/day on the first day and 400 mg/day thereafter) was started 23 days after the operation.

Follow-up CT in August 2008 showed no residual lesion with partial thickening of the mucosa (Fig. 3e). CT in November 2008 showed opacification of the left sphenoid sinus (Fig. 3f). Re-operation with sphenoidotomy was performed. The sphenoid sinus was filled with serous fluid and the mucosa of the natural ostium was slightly edematous. However, a biopsy specimen showed no evidence of Aspergillus invasion. The sphenoid sinus is observable with fiber scope and examined regularly. The patient has since been taking voriconazole for 8 months without recurrence.

2.3. Case 3

A 78-year-old woman with a history of hypertension, arrhythmia, and neurogenic bladder was referred to our hospital in June 2008 for left maxillary sinus lesion confirmed with CT.

Coronal CT with contrast medium demonstrated a hypodense mass and small calcification in the left maxillary sinus. The maxillary sinus was partially aerated. The roof and the medial wall of the maxillary sinus were absorbed. The enhanced lesion had invaded the ethmoid sinus and orbit (Fig. 4a). Axial CT demonstrated the absorbed medial maxillary wall (Fig. 4b). MR imaging was not possible because the patient had an artificial pacemaker. Calcification in the maxillary sinus indicated fungal ball. Surgery was performed trans-nasally and trans-antrally. Fungal ball and yellow mucus filled the maxillary sinus. The mucosa of the roof of the maxillary sinus was hypertrophic. Histological examination of the fungus ball and edematous mucosa of the roof of the maxillary sinus revealed Aspergillus in the...
mucosa. Systemic voriconazole administration (loading dose 600 mg/day on the first day and 400 mg/day thereafter) was started 8 days after the operation.

Follow-up CT in September 2008 and February 2009 showed the maxillary and ethmoid sinuses remained clear and the lesion in the orbit had diminished. Coronal CT showed the maxillary sinus and the ethmoid sinus were clear after 2 months of voriconazole administration. The large opening of the antrostomy was maintained. The intraorbital lesion had diminished significantly (Fig. 4c). Coronal CT after 7 months of voriconazole administration showed the intraorbital lesion had disappeared completely (Fig. 4d). Voriconazole administration was discontinued in February 2009 after a total of 7 months of voriconazole administration.

3. Discussion

Recently, new systemically administered antifungal agents have been approved for clinical use. Voriconazole is a second generation triazole with a broad spectrum of antifungal activity against *Candida, Aspergillus, Cryptococcus*, and other species, with superior effectiveness for invasive aspergillosis compared to amphotericin B [7]. Voriconazole is a suitable alternative to amphotericin B.
preparations for empirical antifungal therapy in patients with neutropenia and persistent fever [8]. Therefore, voriconazole has been recommended in international guidelines as the primary therapy for acute invasive aspergillosis [9]. However, invasive fungal sinusitis is rare compared to pulmonary invasive aspergillosis, so any evidence-based treatment is difficult to recommend. Only a few case reports have described the clinical course of invasive fungal sinusitis treated with new antifungal agents [10–12]. A 12-year-old girl with diabetes mellitus who had invasive fungal ethmoiditis with *Rhizopus* species extending to the orbit and frontal lobe successfully treated with the new triazole posaconazole for 15 months [12]. Four cases of invasive sphenoidal aspergillosis were treated with spheno- dotomy and 3-month administration of voriconazole (400 mg/day) [11]. Two of these patients received administration of amphotericin B which was soon discontinued because of renal side effects before treatment with voriconazole. One patient received combination therapy with caspofungin and voriconazole for the first 3 days [11]. An 89-year-old woman with invasive ethmoidal aspergillosis extending to the nasopharynx, infratemporal fossa, orbit, and cavernous sinus was treated with the combination of caspofungin (loading dose 70 mg/day and 50 mg/day thereafter) and voriconazole (loading dose 12 mg/kg per day and 8 mg/kg per day thereafter) for several months [10].

The present three cases of chronic fungal sinusitis were successfully treated with surgery and voriconazole administration. All patients were immunocompetent and had chronic invasive aspergillosis. Case 1 underwent subtotal removal of the maxillary mucosa because the diagnosis had been established before the operation. The lesion in the orbit was left untouched to avoid complications to his normal sight. Systemic micafungin infusion for 1 month did not provide therapeutic response. On the other hand, voriconazole improved cheek pain within a few weeks. The difference of efficacy may indicate the superiority of voriconazole over micafungin. Cases 2 and 3 underwent surgery under diagnoses of non-invasive fungal sinusitis, and the diagnosis of invasive fungal sinusitis was only confirmed later with the analysis of the biopsy specimen. Therefore, complete removal of the affected tissue was not achieved in any case. Neuroimaging and endoscopic examination indicated that the unresected lesions in all three patients continued to diminish during voriconazole administration.

The optimal duration of antifungal drug administration for chronic invasive fungal sinusitis is controversial, and reports vary widely depending on the severity of the disease and institution from 3 months to more than 15 months [10–12]. Case 3 received administration of voriconazole for 7 months, and Cases 1 and 2 have continued to receive voriconazole for 8 months and ongoing. The biopsy specimen taken at the second
surgery in Case 2 was free of fungal hyphae. The discontinuation of voriconazole is an open question. We have continued administration considering the risk of recurrence and the safety of voriconazole to the patient.

Case 1 experienced mild liver dysfunction 7 weeks after the initiation of voriconazole. After consultation with a gastroenterologist, the dose of voriconazole was reduced to 300 mg/day. Drug-induced liver dysfunction was suspected. One week after the reduction of voriconazole dose, the liver dysfunction was relieved. The same laboratory study showed the serum potassium level increased to 6.1 mmol/L. A nephrologist was consulted. Potassium-restricted diet improved the ion balance of the blood serum. No side effect was encountered thereafter. Cases 2 and 3 have been taking voriconazole without any side effects. We recommend that liver function should be checked regularly when administering voriconazole. Neuroimaging studies such as CT and MR imaging with contrast medium are reliable methods to monitor the clinical course.

4. Conclusion

Voriconazole is a new antifungal agent effective against invasive aspergillosis. Three cases of chronic invasive fungal sinusitis were treated successfully with subtotal surgical removal and extended voriconazole administration. All patients had good clinical outcome. Voriconazole use for invasive fungal sinusitis may create the opportunity to change the conventional treatment approaches based on amphotericin B.

References