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# Invasive Sphenoidal Aspergillosis: Successful Treatment with Sphenoidotomy and Voriconazole

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**Key Words**
Voriconazole · Invasive aspergillosis · Sphenoid sinus · Sphenoidotomy

**Abstract**
Treatment of invasive sphenoidal aspergillosis is surgical, followed by antifungal therapy, mostly amphotericin B. To optimize the adjuvant antifungal treatment, which is often limited by severe side effects, the new triazole antifungal agent voriconazole with broad coverage of fungal pathogens including *Aspergillus* was investigated in a study of 4 patients with clinical, radiological and histological signs of invasive sphenoidal aspergillosis. They first underwent endoscopic sphenoidotomy with drainage and extraction of the fungal mass. Postoperatively, 2 patients were immediately treated with voriconazole. Two patients initially received amphotericin B; but this treatment had to be stopped because of acute renal toxicity. Finally, all patients were treated orally with 200 mg voriconazole twice a day for 12–14 weeks. After this combined treatment all patients were asymptomatic and there were no endoscopic or radiological signs of residual fungal disease. The only side effects were nausea in one and transient visual disturbances in 2 other patients. In the 4 patients presented and treated, voriconazole was shown to be effective and less toxic than amphotericin B in adjuvant treatment of invasive sphenoidal aspergillosis.



## Introduction

Invasive sphenoidal aspergillosis is a rare but potentially life-threatening disease. It can be divided into an acute fulminant form with rapid and often fatal disease progression in immunocompromised patients and a chronic nonfulminant but invasive form. The latter is characterized by an indolent course with slow disease progression and delayed diagnosis in immunocompetent or only mildly immunocompromised patients with diabetes mellitus or corticosteroid treatment [1]. A granulomatous and a nongranulomatous form have been recognized [2]. In Europe, the more common nongranulomatous form is mostly caused by *Aspergillus fumigatus* [1, 2].

Chronic *Aspergillus* sinusitis has a tendency to invade adjacent structures. Consequently, the typical history is a chronic sinusitis with diffuse headache and rhinorrhea

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for months or years, followed by sudden visual disturbances or ocular motion impairment resulting from an orbital apex or a cavernous sinus syndrome. Involvement of the cavernous sinus with fungal thrombosis has a high mortality rate [1] and mycotic aneurysms or ruptures of the internal carotid artery are known severe complications [3].

Due to unspecific clinical symptoms, diagnosis is often suspected on imaging studies, but has to be confirmed by microbiology and histopathology to demonstrate the fungus and to document the invasive nature with infiltrated hyphal forms within the sinus mucosa, submucosa, blood vessels, bone or nerves [4, 7]. Computed tomography (CT) and magnetic resonance imaging (MRI) are highly sensitive diagnostic tools, being able to identify sinus inflammation and alterations of surrounding structures at high-resolution rates. In addition, their ability to detect ferromagnetic substances (such as iron, manganese and magnesium) as well as calcium deposits in the paranasal sinus may provide the first indication of a fungal cause of the sinusitis [5].

The treatment of choice for invasive sphenoidal aspergillosis is surgical debridement, followed by antifungal therapy. Until recently, radical surgical approaches with complete extraction of the mucosa were recommended [1, 6] and amphotericin B was considered the drug of choice for the treatment of invasive fungal disease. However, the use of amphotericin B is frequently limited by its nephrotoxicity that often necessitates the adjuvant medical therapy to be stopped or changed. Therefore, the new antifungal agent voriconazole, which has broad coverage of fungal pathogens, including *Aspergillus* species, and a more favorable profile of adverse effects, was investigated to optimize antifungal treatment in a surgical approach with less radical sphenoidectomy, i.e. without resection of the mucosa ('conservative' sphenoidotomy).

Voriconazole (Vfend®, Pfizer, New York, US) is a new second-generation triazole, which is fungicidal for all *Aspergillus* species and has documented efficacy against invasive aspergillosis [7]. The compound has excellent penetration characteristics into all tissues including brain and bone [8, 9]. Intravenous and oral formulations are available. Oral bioavailability exceeds 90%. Metabolization via the cytochrome P-450 enzyme system is the drug's dominant mechanism of elimination, thus drug interactions must be considered. Voriconazole is well tolerated; the most common adverse effects are transient visual disturbances in 20–40%, increased liver function tests in 10% and photosensitivity and rashes in 15% [10].

## Material and Methods

In this study, conducted between 2002 and 2005, we report 4 immunocompetent patients aged 29–72 years, with chronic invasive aspergillosis (fig. 1, 2). All patients suffered from chronic headaches for more than 5–10 months. Patients 1, 3 and 4 additionally suffered from acute cranial nerve palsy and patient 2 from hyperprolactinemia, leading to a radiologic examination. No patient received systemic corticosteroids during the year previous to our treatment and none was suffering from diabetes mellitus. The tentative diagnosis of invasive fungal sinusitis was based on imaging studies and confirmed by micro- and histopathology. CT and MRI were carried out in all patients as complementary exams for evaluation of hard and soft tissues of the paranasal sinus and their surrounding structures as well as the skull base. Preoperatively, all patients underwent a nasal endoscopy, which revealed retention of purulent secretion in the sphenoidal recess in case 3 only.

The surgical procedure consisted of a direct transnasal endoscopic sphenoidotomy with enlargement of the sphenoidal ostium, extrusion of purulent and pasty secretions, fungal elements and inflammatory tissue masses, but without radical extraction of the sphenoidal mucosa. For improved sphenoidal drainage and better visibility during follow-up, a partial resection of the middle turbinate was performed in three patients. *Aspergillus* spp. was identified as the causative organism in all patients by either culture (patient 2) or PCR (patients 1, 3 and 4) performed on material retrieved intraoperatively from the sphenoidal sinus, and the invasive process by histopathology with fungal invasion within sinus mucosa (Gomori methenamine silver stain).

Postoperatively, antifungal treatment was started with voriconazole in patients 3 and 4 (intravenously for the first 3 days at 4 mg/kg q12 h, 6 mg/kg q12 h for the first 2 doses), patient 3 was given a combination therapy with i.v. voriconazole and caspofungin (3 days 50 mg intravenously), because of the acuteness of the disease process. Patients 1 and 2 first received amphotericin B, because pending microbiology results and Mucorales could not be ruled out as the causative organisms during the first days (voriconazole has no activity against Mucorales). Amphotericin B was stopped in both patients after 6 and 12 days due to acute renal toxicity. When i.v. drugs were discontinued, all patients received 200 mg of voriconazole orally b.i.d. for 3 months.

Local treatment of the nose consisted of irrigation with saline solution (Rhinomer™, Novartis, Basel, Switzerland) and application of dexpanthenolum nasal crème (Bepanthen®, Roche, Basel, Switzerland) as well as weekly suction cleansing of the nose and sphenoidal region in our out-patient clinic. The follow-up examinations included nasal endoscopy of the surgically enlarged sphenoidal ostium and the sinus as well as MRI or CT 3 and 6–12 months after treatment to exclude a persisting or new opacification, hyperdense foci or hypointense signals within the paranasal sinus.

## Results

The patients symptoms, findings of CT and MRI examinations, microbiology and histopathology results, as well as the clinical and radiological follow-up studies are

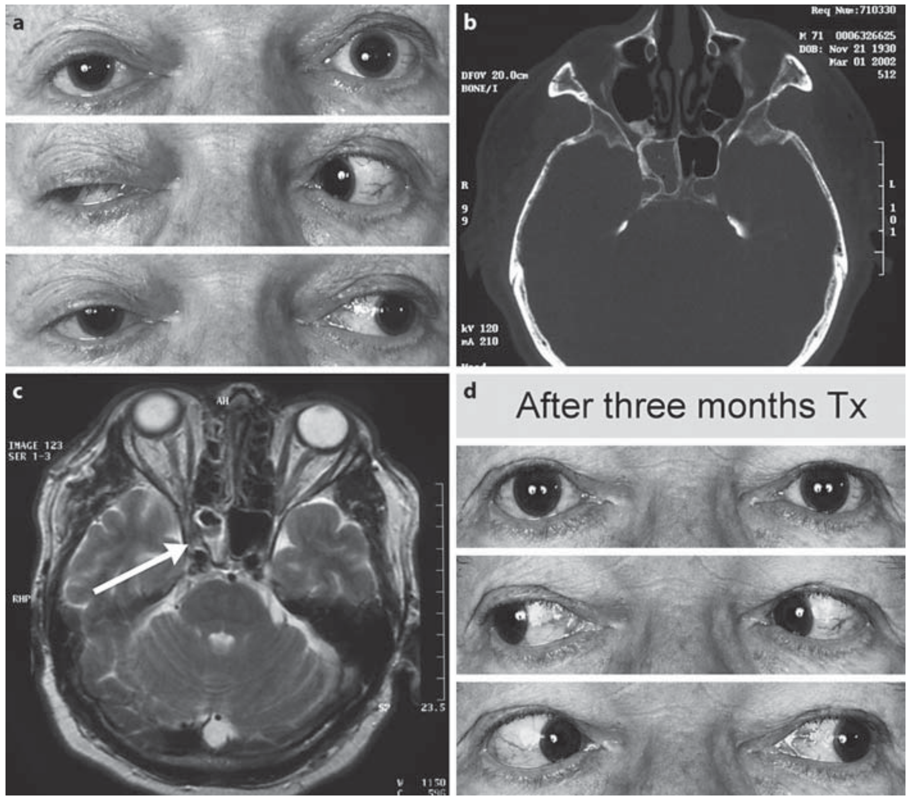


**Fig. 1.** Patient 1 who had chronic headache for 6 months, rhinorrhea, visual disturbances for colors, and diplopia. **a** Palsy of right oculomotorius nerve with ptosis, mydriasis and bulbus rotation downward and toward the temporal side. **b** Axial CT shows a hypodense expanding mass and small calcifications in the right sphenoidal sinus. **c** Axial MRI (T2-weighted sequence) shows fungal invasion of the cavernous sinus (arrow). **d** Normal bulbus motility and vision after 3 months of combined treatment.

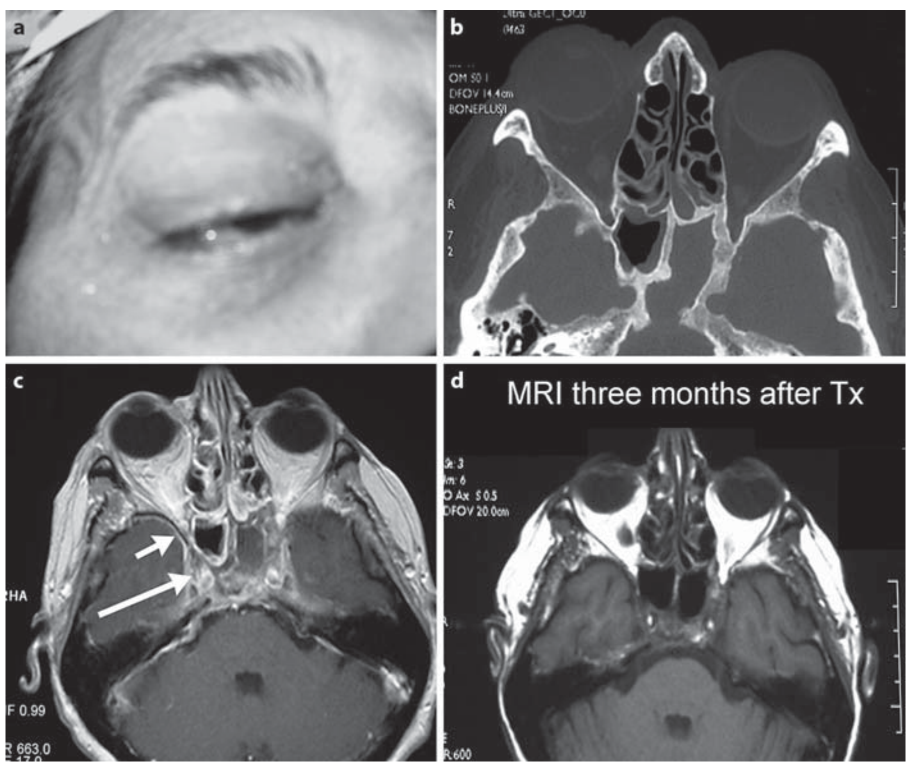


**Fig. 2.** Patient 3 with acute onset of high fever, severe diffuse headache and diplopia due to abducens palsy. **a** Bulbus protrusion and chemosis of the right eye. **b** Axial CT with hyperdense mass destroying the clivus. **c** Axial MRI suggests infiltration of the contralateral cavernous sinus by fungal mass (arrow) and a leptomeningeal enhancement (small arrow). **d** Axial follow-up MRI 3 months after discontinuation of treatment shows no signs of recurrence.

**Table 1.** Overview of patients' symptoms, evidence of invasive disease, microbiological and histological data from extracted tissue

| Patient | Symptoms | Evidence of invasive disease | Microbiology, PCR test, histopathology (HP) |
|---|---|---|---|
| 1 ♂ (fig. 1) | chronic headache, diplopia, impaired color vision, ptosis and mydriasis due to palsy of N III | fungal invasion of cavernous sinus (clinic and MRI) fungal invasion of mucosa (HP) | *Aspergillus fumigatus* |
| 2 ♀ | chronic headache, amenorrhea, failure to get pregnant, hyper-prolactinemia 41.3 μg/l (ref. <20) | lateral and dorsal sphenoidal bone erosion (CT) fungal invasion of mucosa (HP) | *Aspergillus fumigatus* |
| 3 ♀ (fig. 2) | high fever, severe headache, diplopia due to palsy o VI, protrusion of bulbus, chemosis | invasion of contralateral cavernous sinus, thrombosis of sup ophthalmic vein, leptomeningeal enhancement (clinic and MRI), destroyed clivus (CT) | *Aspergillus* sp. |
| 4 ♀ | chronic headache, rhinorrhea; acute diplopia due to palsy of N III and IV, facial pain | bone erosion of clivus and carotis canal (CT); invasion of cavernosus sinus (clinic and MRI) fungal invasion of mucosa (HP) | *Aspergillus fumigatus* |

**Table 2.** Overview of antifungal treatment, side effects of voriconazole, and clinical and imaging follow-up

| Patient | Treatment with amphotericin B | Treatment with i.v. voriconazole | Treatment with oral voriconazole | Side effects of voriconazole | Follow-up clinical signs and imaging studies 3, 6 and 12 months after treatment |
|---|---|---|---|---|---|
| 1 ♂ (fig. 1) | 12 days i.v. (50 mg qd) | | 3 months oral (200 mg b.i.d.) | transient visual disturbances | normal vision and bulbus movement (3 months) CT/MRI: no remaining disease or recurrence (3, 6, 12 months) |
| 2 ♀ | 6 days i.v. (50 mg q.d.) | | 3 months oral (200 mg b.i.d.) | transient visual disturbances | normal prolactin level (15.8 μg/l), no headaches CT/MRI: no signs of recur-rence (6, 12 months) |
| 3 ♀ (fig. 2) | none | 10 days i.v. (6 mg/kg b.i.d. day 1; then 4 mg/kg b.i.d.) plus 3 days i.v. caspo-fungin 50 mg q.d. | 3 months oral (200 mg b.i.d.) | nausea, 5 kg weight loss | normal bulbus motility (3 months) MRI: no signs of recurrence (6, 12 months) |
| 4 ♀ | none | 3 days intravenous (6 mg/kg b.i.d. day 1; 4 mg/kg b.i.d. days 2–3) | 3 months oral (200 mg b.i.d.) | none | asymptomatic, normal bulbus motility (3 months) CT: no signs of recurrence (6 months) |

summarized in tables 1 and 2. *Aspergillus* spp. was found by microbiological examination (either by culture or by PCR-test) in every patient, as well as fungal hyphae in the extracted tissue and sinus mucosa in histopathology.

Voriconazole was generally well tolerated during the 3 months of treatment. Side effects were noted in 3 patients; cases 1 and 2 had transient visual disturbances lasting minutes to hours after drug intake, with complete recovery thereafter. Case 3 experienced nausea and lost 5 kg in weight. No patient had pathologic liver function tests or rashes (table 2). All patients had complete recovery of their symptoms without any signs of remaining fungal disease in imaging studies 3 months after combined treatment and no signs of recurrent disease after 6–12 months (fig. 1, 2).

## Discussion

Invasive sphenoidal aspergillosis is a rare disease. Diagnosis is often delayed by nonspecific clinical manifestations and poor accessibility of the sphenoid sinus during physical and endoscopic examination. It is not uncommon that diagnosis is only established in a late stage when complications that stem from invasion of surrounding structures by the fungi and the accompanying inflammatory reaction have already occurred. Commonly involved are the cavernous sinus (as in our patients 1 (fig. 1), 3 (fig. 2) and 4) or the orbital apex, their involvement manifesting itself by visual disturbances as a consequence of alterations of the optic nerve (patient 1) or palsy of the cranial nerves III to VI. Apart from the optic nerve, the abducens nerve is the next commonly affected nerve (as in patients 3 and 4), probably due to its long and medial pathway in the cavernous sinus [11, 12]. After penetration of the dura, sphenoidal aspergillosis can also invade the sella turcica and may result in hyperprolactinemia by pituitary abscess formation, compression of the pituitary-hypothalamic axis when extending into the suprasellar area or by direct irritation of the pituitary gland as result of chronic sphenoidal inflammation (as seen in patient 2) [13]. In immunocompromized patients, e.g. following solid organ transplantation, chronic sphenoidal aspergillosis can develop into an acute fulminant and often fatal disease with extension into the skull base and the brain.

Recent improvements in imaging techniques facilitate the diagnosis. On CT, patients with chronic fungal sinusitis often show hyperdense foci of increased attenuation due to calcium phosphate and calcium sulfate. However, in less chronic courses, these indications can be absent. The most sensitive and specific signs for fungal sinusitis found in MRI are hypointense signals in a $T_1$-weighted image, becoming very hypointense in the $T_2$ sequence. This phenomenon seems to be due to the presence of ferromagnetic elements like iron and manganese within fungal concretions [14, 15].

In noninvasive chronic aspergillosis, the treatment of choice is surgery with extrusion of the fungal mass. When aspergillosis is invasive, it is imperative that surgery is followed by antifungal medication [16]. In the last decades, amphotericin B has been the gold standard for treating invasive aspergillosis [1, 10] and is still often chosen because of its broad antifungal spectrum in severe mold infection, when the causative organism is not yet known. Diagnosis can be suspected by the clinical aspect during surgery but needs confirmation by histology and microbiological methods, the results of which are available after 3–4 days. Cultures can be falsely negative in 40–50% of the cases (in our case series 75%) [1, 18] and histopathological confirmation can be difficult when only necrotic tissue is obtained in biopsies [17], as observed in other cases not part of this study. However, histopathology is evident to confirm or exclude an invasive fungal process, as well as to differentiate from other pathologies with radiological bone erosions as seen, e.g., in an allergic fungal rhinosinusitis [19]. But even in negative biopsies, the possibility of an invasive mycosis must be kept in mind in patients with an erosive and destructive mass involving the cavernous sinus or the orbital apex [1, 17] with a rapid decision of an antifungal treatment due to its high mortality. Amphotericin B, not being available for oral application, is associated with a high rate of nephrotoxicity (as seen in patients 1 and 2) and infusion reactions. Voriconazole, in contrast, is generally well tolerated and distributes well into all tissues including brain and bone, with tissue concentrations that may exceed plasma concentration [8, 9, 20, 21]. This property is important in the treatment of invasive sphenoidal aspergillosis which often erodes bone and may invade both meningeals and brain. For the treatment of invasive aspergillosis in hematopoietic cancer patients, voriconazole was even shown to have superior efficacy and survival rates compared to amphotericin B [7, 22]. Nevertheless, the high daily costs of voriconazole (EUR 89.– per day) remains a disadvantage. In comparison, however, the lipid associated formulations of amphotericin B, which are better tolerated than conventional amphotericin B, are even more expensive.

All our patients had complete resolution of all signs and symptoms of infection and no evidence of recurrent disease at follow-up. This limited experience suggests that a three months treatment course of invasive sphenoidal aspergillosis is sufficient. Incidentally, the same treatment duration is commonly used for chronic bacterial osteomyelitis.

Concerning sphenoidotomy, the goal of our surgical approach was to enlarge the entrance to the sphenoid and to completely remove the fungal mass and necrotic tissue from the sphenoid sinus with forceps and irrigation. No attempt was made to resect the mucosa too. Fungal invasion of mucosa, bone and cavernous sinus was eradicated by adjuvant medical therapy. This was successful in all our cases. Other authors recommend a radical sphenoidectomy with total extirpation of the mucosa [6]. In view of our results, the optimal surgical procedure for invasive sphenoidal aspergillosis should be reviewed and we see chances for a less radical surgical approach.

In conclusion, voriconazole in combination with a sphenoidotomy that preserves the mucosa was an effective treatment in 4 cases with invasive sphenoidal aspergillosis and was better tolerated than amphotericin B. This combined approach appears to be an interesting alternative to radical sphenoidectomy in combination with amphotericin B.

## References


1 DeShazo RD, Chapkin K, Swain RE: Current concepts in fungal sinusitis. N Engl J Med 1997;337:254–259.
2 Fatterpekar G, Mukherji S, Arbealez A, Maheshwari S, Castillo M: Fungal diseases of the paranasal sinuses. Semin Ultrasound CT MR 1999;20:391–401.
3 Corvisier N, Gray F, Gherardi R, Lebras F, Blanc CM, Nguyen JP, Poirier J: Aspergillosis of the ethmoid sinus and optic nerve with arteritis and rupture of the internal carotid artery. Surg Neurol 1987;28:311–315.
4 Stringer SP, Ryan MW: Chronic invasive fungal rhinosinusitis. Otolaryngol Clin N Am 2000;33:375–387.
5 Nicolai P, Tomenzoli D, Berlucchi M, Redaelli LO, Maroldi R, Antonelli AR: Il trattamento endoscopico dell' aspergilloma sfenoidale. Acta Otorhinolaryngol Ital 1998;18:23–29.
6 Petrick M, Honegger J, Daschner F, Feuerhake F, Zentner J: Fungal Granuloma of the sphenoid sinus and clivus in a patient presenting with cranial nerve III paresis: case report and review of the literature. Neurosurgery 2003;52:955–958.
7 Herbrecht R, Denning DW, Patterson TF, Bennett J, Greene RE, Oestmann J-W, Kern WV, Maar KA, Ribaud P, Lortholary O, Sylvester R, Rubin RH, Wingard JR, Stark P, Durand C, Caillot D, Thiel E, Chandrasekar PH, Hodges MR, Schlamm HAT, Troke PF, de Pauw B: Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 2002;347:408–415.
8 Purkins L, Wood N, Gharamani P, Greenhalgh K, Allen MJ, Kleinermans D: Pharmacokinetics and safety of voriconazole following intravenous- to oral-dose escalation regimes. Antimicrob Agents Chemother 2002;46:2546–53.
9 Lortholary O, Mouas-Dupuy H, Dupont B, Lutsar I, Fain O: Voriconazole for bone aspergillosis: a worldwide experience of 19 cases. Abstract on 14th Congress of European Society of clinical Microbiology and Infectious Diseases, Prague, 2004.
10 Gothard P, Rogers TR: Voriconazole for serious fungal infections. Int J Clin Pract 2004; 58:74–80.
11 Lawson W, Reino AJ: Isolated sphenoidal sinus disease: an analysis of 137 cases. Laryngoscope 1997;107:1590–1595.
12 Sethi D: Isolated sphenoid lesions: diagnosis and management. Otolaryngol Head Neck Surg 1999;120:730–736.
13 Lecanu JB, Lissak B, Halimi Ph, Bonfils P: Sphénoidite chronique responsable d'une hyperprolactinémie. Rev SFORL 2004;82: 34–35.
14 Zinreich SJ, Kennedy DW, Malat J, Curtin HD, Epstein JI, Huff LC, Kumar AJ, Johns ME, Rosenbaum AE: Fungal sinusitis: diagnosis with CT and MR imaging. Radiology 1988;169:439–444.
15 Ishibashi T, Kikuchi S: Mucocele-like lesions of the sphenoid sinus with hypointense foci on $T_2$-weighted magnetic resonance imaging. Neuroradiology 2001;43:1108–1111.
16 Washburn RG: Fungal sinusitis. Curr Clin Top Infect Dis 1998;18:60–74.
17 Dhiwakar M, Thakar A, Bahadur S: Invasive sino-orbital aspergillosis: surgical decisions and dilemmas. J Laryngol Otol 2003;117: 280–285.
18 Clancy CJ, Nguyen MH: Invasive sinus aspergillosis in apparently immunocompetent hosts. J Infect 1998;37:229–240.
19 Nussbaum B, Marple BF, Schwade ND: Characteristics of bony erosions in allergic fungal rhinosinusitis. Otolaryngol Head Neck Surg 2001;124:150–154.
20 Stratov I, Korman TM, Johnson PD: Management of aspergillus osteomyelitis. Report of failure of liposomal amphotericin B and response to voriconazole in an immunocompetent host and literature review. Eur J Clin Microbiol Infect Dis 2003;22:277–283.
21 Klastersky J: Empirical antifungal therapy. Int J Antimicrob agents 2004;23:105–112.
22 Denning DW, Ribaud P, Milpied N, Caillot D, Herbrecht R, Thiel E, Haas A, Ruhnke M, Lode H: Efficacy of voriconazole in treatment of acute invasive aspergillosis. CID 2002;34:356–371.