Mortality Rate and Predictive Factors for Invasive Fungal Rhinosinusitis: Experience in Siriraj Hospital

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ABSTRACT

Objective: To elucidate the mortality rate and prognostic factors in patients with invasive fungal rhinosinusitis in Siriraj Hospital.

Methods: Thirty-nine patients with a definitive diagnosis of invasive fungal rhinosinusitis were recruited from October 2003 to September 2014. The mortality rate was retrieved, and the impacts of underlying diseases, clinical presentation, disease extension, fungal types, antifungal drugs, and time to treatment were statistically analyzed.

Results: The overall mortality rate was 23.1%. All patients except one were immunocompromised. Cranial nerve involvement was the most common symptom. The ethmoid sinus was the most commonly affected intranasal site (46.2%), and the majority of extranasal lesions were located in the orbit (17.9%). Most patients were affected by *Aspergillus* spp. (64.1%). Alteration of consciousness and periorbital pain were significant negative prognostic factors [adjusted odds ratio (95% confidence interval), 10.37 (1.31–82.07) and 8.67 (1.30–57.88), respectively]. Other factors such as time to treatment, age, and central nervous system involvement had no effect on mortality.

Conclusion: The mortality rate of invasive fungal rhinosinusitis in this study was 23.1%. Negative prognostic factors were alteration of consciousness and periorbital pain. Clinicians must have a high index of suspicion for invasive fungal rhinosinusitis, and aggressive treatment should be considered.

Keywords: Invasive fungal rhinosinusitis; fungal infection; mucormycosis; aspergillosis; prognosis; mortality (Siriraj Med J 2018;70: 36-43)

INTRODUCTION

Fungal infections of the paranasal sinuses are divided into 2 forms: noninvasive and invasive disease. The noninvasive form is more common and causes chronic rhinosinusitis. In contrast, the invasive form is rapidly progressive and occurs in immunocompromised patients[1,2] such as those with diabetes, prolonged steroid use, and neutropenia. Patients with invasive fungal disease frequently present with more severe symptoms of rhinosinusitis, including fever, facial edema, nasal stuffiness, and discolored nasal discharge. Invasive fungal rhinosinusitis (IFRS) was recently found to be more common than in the past,[3] with high mortality rates ranging from 50% to 80%.[1,2,4]

Early diagnosis of invasive disease is crucial, especially in immunocompromised patients. Pathological examination of suspicious tissue with pathogen identification is mandatory for a definite diagnosis of IFRS. Common causative pathogens are *Aspergillus* spp. and Zygomycetes genera (*Mucor* spp., *Rhizopus* spp., *Rhizomucor* spp.).[1,2] However, culture is the gold standard diagnostic test for identification of fungal species. Surgical intervention is the most important treatment in patients with IFRS. Adequate debridement of infected tissue with systemic

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antifungal agents and treatment of comorbid diseases provides better results.[4-6]

According to previous studies, negative prognostic factors in patients with IFRS are higher age, central nervous system involvement, changes in consciousness, a delay in starting antifungal drug treatment, and inadequate tissue debridement.[1,2] In a recent systematic review of 52 articles, Turner et al.,[1] studied the mortality rate and risk factors for IFRS in 807 patients and found that the mortality rate was 46.1% and that older age and central nervous system involvement were significant risk factors. Patients with diabetes mellitus had the lowest mortality rate among all comorbidities. Chen et al.,[7] reviewed IFRS comorbidities in 46 patients with hematologic malignancies and found a mortality rate of 41.3%. IFRS developed more commonly in patients with acute myeloid leukemia with prolonged neutropenia.

The mortality rate of IFRS in Thailand varies across different published case series and reports, ranging from 20.0% to 44.7%.[2,8] Soontrapa et al.,[2] reported that the most common coincidental disease was hematologic malignancy. Piromchai and Thanaviratananich[9] studied the impact of the treatment start time in patients with acute IFRS. The study showed an association between the treatment start time and the mortality rate. Starting treatment within 14 days of onset significantly decreased the mortality rate. Patients with IFRS historically received amphotericin B after pathological examination demonstrated tissue invasion by a fungus. The new drug voriconazole was reserved only for patients with a positive *Aspergillus* culture. Infectious disease specialists now tend to prescribe antifungal drugs earlier in the disease course when IFRS is suspected while awaiting a definitive tissue diagnosis. Moreover, voriconazole is now frequently used when the pathologic findings are compatible with *Aspergillus* spp., despite a negative culture. Based on this changing paradigm, we hypothesize that outcomes will improve and mortality will decrease. In the present study, we analyzed the mortality of and predictive factors for IFRS. We also present data that are lacking in other studies,[2,8,9] such as how the site of disease involvement as determined by nasal endoscopy compares with the radiographic and pathologic findings, advanced identification of fungal species by polymerase chain reaction (PCR), and the effects of new antifungal drugs (voriconazole and posaconazole) on the mortality rate.

MATERIALS AND METHODS

This study included 39 consecutive patients with a pathologically confirmed diagnosis of IFRS from October 2003 to September 2014. The Institutional Review Board approved the data collection (Si 808/2556). When tissue culture data were lacking, paraffin blocks of tissue were sent for PCR to identify the type of fungus. The overall mortality rate was presented as a percentage. Prognostic factors were analyzed by the Chi-square test or Fisher's exact test, and any variables with a p-value of <0.05 were selected for multivariate logistic regression. For both univariate and multivariate analysis, a p-value of <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY).

RESULTS

The mortality rate was 23.1%. The 39 patients comprised 19 male and 20 female patients with a mean age of 56.0 ± 15.1 years (range, 5-84 years). The most common underlying disease was diabetes mellitus (69.2%). The other comorbidities were hematologic malignancy (12.8%), human immunodeficiency virus infection (7.7%), systemic lupus erythematosus (5.1%), and CD4 lymphocytopenia (2.6%). Only 1 patient (2.6%) was healthy.

Decreased vision was found in 46.2% of the patients. Headache and periorbital pain were found in 38.5% and 25.6%, respectively. Seven patients (17.9%) had an altered consciousness. Cranial nerve involvement was the most common symptom among all patients (Table 1).

The average admission period was 33 days. The mean time from a provisional diagnosis of IFRS to initiation of systemic antifungal agents and/or surgery was 1.7 and 0.9 days, respectively. Twenty-six patients (68.4%) underwent sinus surgery within 24 hours after the provisional diagnosis, 6 (15.8%) underwent surgery from 24 to 48 hours, and 6 underwent surgery beyond 48 hours. One patient refused to undergo surgery.

With respect to the presentation of signs and symptoms, the patients were divided into a presenting time of ≤28 days (n = 14, 35.9%), 29 to 90 days (n = 10, 25.6%), and >90 days before admission (n = 15, 36.5%).

Physical examination and nasal endoscopy revealed no abnormalities in 4 patients (10.3%). Lesions were confined to the nasal cavity and/or paranasal sinuses in 12 patients (30.7%). The lesions extended to surrounding organs in 23 patients (59.0%) (Table 2). The most common site of involvement was the orbit (46.2%). The lesion distribution rate was 33.3% each in the ethmoid, maxillary, and sphenoid sinuses. Mucosal edema and necrotic tissue were found in 46.2% and 41.2% of patients, respectively. Other findings, such as ulceration, mucosal erythema, bone exposure, and masses, were found in 2.6% to 5.1% of patients.

TABLE 1. Clinical characteristics of patients with invasive fungal rhinosinusitis (n = 39).

Presentation	Patients*
Cranial nerve involvement	19 (48.7)
Decreased vision	18 (46.2)
Headache	15 (38.5)
Periorbital pain	10 (25.6)
Facial pain	7 (17.9)
Alteration of consciousness	7 (17.9)
Facial swelling	6 (15.4)
Nasal congestion	6 (15.4)
Nasal discharge	6 (15.4)
Double vision	5 (12.8)
Fever	4 (10.3)
Epistaxis	3 (7.7)
Cheek numbness	1 (2.6)
Orbital swelling	1 (2.6)
Periorbital swelling	1 (2.6)
Proptosis	1 (2.6)
Seizure	1 (2.6)

Data are presented as n (%). *Some patients probably had more than one sign/symptom.

TABLE 2. Site of involvement in patients with invasive fungal rhinosinusitis.

	Nasal endoscopy/physical examination*	Imaging (CT/MRI)*
Intranasal/PNS lesion		
Ethmoid sinus	13 (33.3)	31 (79.5)
Maxillary sinus	13 (33.3)	25 (64.1)
Sphenoid sinus	13 (33.3)	24 (61.5)
Nasal cavity/septum	11 (28.2)	10 (25.6)
Middle turbinate	10 (25.6)	0 (0.0)
Ostiomeatal unit	2 (5.1)	3 (7.7)
Uncinate process	2 (5.1)	0 (0.0)
Inferior turbinate	1 (2.6)	0 (0.0)
Superior turbinate	1 (2.6)	0 (0.0)
Frontal sinus	0 (0.0)	10 (25.6)
Extranasal/PNS lesion		
Orbit	18 (46.2)	21 (53.8)
Intracranial	6 (15.4)	7 (17.9)
Cavernous sinus	5 (12.8)	4 (10.3)
Palate	4 (10.3)	11 (28.2)
Cheek	2 (5.1)	2 (5.1)

Data are presented as n (%). *Some patients probably had more than one lesion.
Abbreviations: computed tomography = CT, magnetic resonance imaging = MRI, paranasal sinus = PNS

All patients with IFRS in this study had abnormal radiographic findings. Computed tomography or magnetic resonance imaging showed that the lesions were confined to the paranasal sinuses and nasal cavity in only 14 patients (35.9%). The lesions extended to surrounding organs in 25 patients (64.1%). The ethmoid sinus was the most frequently involved paranasal sinus (79.5%) (Table 2). The orbit was the most involved organ outside the nasal cavity and paranasal sinuses (53.8%).

Pathologic examination showed that the ethmoid and maxillary sinuses were the most commonly involved sites (46.2% and 41.0%, respectively) (Table 3). Tissue infarction, vascular invasion, and granulomas occurred in 89.7%, 59.0%, and 7.7% of patients, respectively.

The causative pathogens were identified by tissue culture in 36 patients, and those in the remaining 3 patients were identified by PCR. Positive results were found in 27 patients (culture in 26 and PCR in 1). The fungi in this study were identified as *Aspergillus* spp., Zygomycetes, *Candida* spp., unspecified molds, and *Ramularia* spp. (Table 4).

Treatment options were combinations of surgical interventions and antifungal drugs (Table 5). All patients who underwent nasal and sinus surgery were divided into 3 groups: endoscopic sinus surgery (n = 30), an external approach (n = 3), and a combined endoscopic with external approach (n = 5). The following other extranasal surgical procedures were performed in 11 patients: orbital exenteration (n = 5), craniectomy/craniotomy (n = 2), debridement (n = 2), removal of the orbital wall (n = 1), and internal carotid artery balloon occlusion (n = 1). Thirty-six patients received antifungal drugs. The two most common medications were amphotericin B and voriconazole. Many patients who received voriconazole were administered amphotericin B at the start of treatment before the histological or culture results could be obtained. Some patients were switched from amphotericin B to a lipid formulation or voriconazole because of amphotericin B toxicity.

The mortality rate in this study was 23.1%. Univariate analysis of factors associated with mortality are shown in Table 6. The times to surgery and initiation of antifungal drugs (cut-off at 48 hours) did not affect the results (p = 0.65 and 1.00, respectively). Alteration of consciousness (p = 0.04) and periorbital pain (p = 0.03) had a significant impact on the mortality rate. Both factors were still statistically significant in the multivariate regression model [alteration of consciousness: p = 0.03, adjusted odds ratio (95% confidence interval) = 10.37 (1.31-82.07); periorbital pain: p = 0.03, adjusted odds ratio (95% confidence interval) = 8.67 (1.30-57.88).

TABLE 3. Site of involvement in patients with invasive fungal rhinosinusitis by pathological finding.

Location	Patients*
Ethmoid sinus	18 (46.2)
Maxillary sinus	16 (41.0)
Nasal septum	8 (20.5)
Middle turbinate	7 (17.9)
Sphenoid sinus	7 (17.9)
Orbit	7 (17.9)
Inferior turbinate	6 (15.4)
Uncinate process	4 (10.3)
Floor/lateral wall of nasal cavity	2 (5.1)
Superior turbinate	1 (2.6)
Frontal sinus	1 (2.6)
Ostiomeatal unit	1 (2.6)
Eustachian tube	1 (2.6)
Nasopharynx	1 (2.6)
Posterior choana	1 (2.6)
Cheek	1 (2.6)
Gingivobuccal sulcus	1 (2.6)

Data are presented as n (%). *Some patients probably had more than one lesion.

TABLE 4. Fungal identification from tissue culture and polymerase chain reaction.

	Patients*
Culture	
Negative	10 (25.6)
Positive	26 (66.7)
Aspergillus spp.	15 (38.5)
Aspergillus fumigatus	5 (12.8)
Aspergillus flavus	2 (5.1)
Aspergillus nigar	3 (7.7)
Zygomycetes	9 (23.1)
Not specified	5 (12.8)
Candida spp.	3 (7.7)
Mold	3 (7.7)
PCR	
Negative	2 (5.1)
Positive (*Ramularia* spp.)	1 (2.6)

Data are presented as n (%). *One patient was infected by two types of fungi simultaneously.

TABLE 5. Treatment options and outcomes.

	Patients
Intranasal/paranasal sinus surgery	
Endoscopic sinus surgery only	30 (76.9)
External approach only	3 (7.7)
Combined approach	5 (12.8)
No surgery	1 (2.6)
Extranasal/paranasal sinus surgery	
Orbital exenteration	5 (12.8)
Craniotomy or craniectomy	2 (5.1)
Debridement	2 (5.1)
Partial removal of orbital wall	1 (2.6)
Internal carotid artery balloon occlusion	1 (2.6)
Antifungal drug*	
Amphotericin B	32 (82.1)
Voriconazole	14 (35.9)
Itraconazole	8 (20.5)
Amphotericin B (lipid formulation)	5 (12.8)
Posaconazole	3 (7.7)
Supersaturated potassium iodide	2 (5.1)
No antifungal drug	3 (7.7)
Outcome	
Survival	30 (76.9)
Death	9 (23.1)

Data are presented as n (%). *Some patients received more than one antifungal drug.

TABLE 6. Univariate analysis of factors associated with mortality.

	Mortality rate (%)	OR (95% CI)	p-value
Underlying disease			
Hematologic malignancy	60.0	7.00 (1.00–51.45)	0.07
HIV infection	33.3	1.75 (0.14–21.88)	0.56
Diabetes mellitus	18.5	0.46 (0.10–2.13)	0.42
Autoimmune disease	0.0	1.00	-
CD4 lymphocytopenia	0.0	1.00	-
Presentation			
Neutropenia	66.7	8.29 (0.66–104.89)	0.13
Alteration of consciousness	57.1	7.20 (1.22–42.49)	0.04
Periorbital pain	50.0	6.25 (1.23–31.84)	0.03
Facial swelling	50.0	4.50 (0.72–28.01)	0.12
Cranial nerve palsy	31.6	2.61 (0.55–12.48)	0.27
Headache	20.0	0.75 (0.16–3.59)	1.00
Extension of disease			
Orbit	33.3	4.00 (0.71–22.51)	0.14
Intracranial	28.6	1.43 (0.23–9.01)	0.65
Cavernous sinus	27.3	1.38 (0.28–6.84)	0.69
Palate	25.0	1.13 (0.10–12.36)	1.00
Cheek	0.0	1.00	-
Organism			
Zygomycetes	50.0	4.00 (0.64–25.02)	0.15
Aspergillus spp.	13.3	0.31 (0.05–1.76)	0.25
Pathology			
Vascular invasion	34.8	6.94 (0.76–63.05)	0.11
Therapy			
Posaconazole	66.7	8.29 (0.66–104.89)	0.13
Liposomal amphotericin B	40.0	2.57 (0.36–18.49)	0.57
Extrasinus surgery	36.4	2.63 (0.55–12.55)	0.24
Amphotericin B	28.1	-	0.17
Voriconazole	14.3	0.43 (0.08–2.43)	0.45
Time from admission to surgery	28.6	1.43 (0.23–9.01)	0.65
Time from admission to drugs	23.1	0.85 (0.17–4.17)	1.00

Abbreviations: odds ratio = OR, confidence interval = CI, human immunodeficiency virus = HIV

DISCUSSION

The patients in our study had a lower mortality rate (23.1%) than patients in other studies (43%-80%).[1,2,4,10-12] Our mortality rate was similar to that in studies by Kasapoglu et al.,[5] and Li et al.,[13] who reported mortality rates ranging from 20% to 30 %. DelGaudio and Clemson[6] and Piromchai and Thanaviratananich[9] reported that early treatment of IFRS significantly decreased the mortality rate. Therefore, our favorable outcome probably resulted from prompt management within 24 hours after the provisional diagnosis, although the difference in the time from admission to surgery and the time from admission

to antifungal treatment was not statistically significant.

In this study, the most common underlying diseases associated with IFRS were diabetes mellitus (69.2%) and hematologic malignancy (12.8%). Turner et al.,[1] reported the lowest mortality rate among patients with diabetes mellitus compared with other underlying diseases. Hematologic malignancy was more common in previous studies.[2-4,11,14]

Blurred vision was a common symptom.[11,15] It was often accompanied by headache, periorbital pain, facial pain, facial edema, nasal stuffiness, and rhinorrhea. We found a large number of patients with nervous system involvement characterized by cranial nerve dysfunction (48.7%) and alteration of consciousness (17.9%). Orbital extension in patients with IFRS was associated with a high mortality rate (33.3%), similar to previous studies by Turner et al.,[1] and Ilica et al.[16] The onset of clinical presentations was prolonged more than 28 days before admission in 25 patients. Our mortality rate was lower than that in previous studies because of the slow disease progression in most of our patients.[1,2,4,7,9-11,14]

In this study, most abnormal findings were identified from nasal endoscopy and radiographic imaging in similar proportions. The exception is that the frontal sinus could not be accessed by nasal endoscopy, and the middle turbinate was very difficult to evaluate by imaging alone. Gillespie et al.,[17] reported that the most common site of involvement was the middle turbinate with a diagnostic sensitivity and specificity of 75% and 100%, respectively.[17] The ethmoid sinus was the most common site of infection based on our pathological reports, and this finding corresponded with the endoscopic and radiographic study findings. Thus, in addition to the middle turbinate, the ethmoid sinus may need to be evaluated when clinicians suspect IFRS.

Tissue culture was beneficial for fungal identification and led to specific antifungal drug administration in this study. Among all 39 patients, the causative fungus was identified by tissue culture in 36 patients and by PCR in 3 patients. *Aspergillus* spp. was the most frequent species in this study. One patient was infected by 2 organisms (*Aspergillus* and *Rhizopus* spp.). PCR provided a positive result in only 1 patient. The negative PCR results might have resulted from disintegration of DNA due to aging of the paraffin block, scant fungus within the tissue, prior antifungal drug administration, improper PCR technique, or misinterpretation of the pathological study findings.

Treatment modalities included surgery, systemic antifungal drug administration, and reversal of the preexisting immunocompromised status. DelGaudio and Clemson[6] concluded that early diagnosis and treatment of IFRS could decrease the mortality rate. Adequate surgical debridement of necrotic tissue is a crucial treatment factor.[7,12] Recent reports have shown equal efficacy between endoscopic and external approaches.[5,12] The endoscopic technique results in less tissue trauma and bleeding and is thus appropriate for early treatment of disease that is limited to the paranasal sinus and nasal cavity.

Amphotericin B is still the first-line drug in the treatment of fungal infection because of its broad-spectrum antifungal activity. It covers *Aspergillus* spp. and Zygomycetes, which are common pathogens in IFRS. Patients with nephropathy have been recommended to change to a lipid formulation of amphotericin B. However, if there is evidence of *Aspergillus* infection, voriconazle is the first-choice treatment instead of amphotericin B.[18,19]

In their systematic review, Turner et al.,[1] studied the prognostic factors for mortality in patients with IFRS and found that advanced age and intracranial involvement were negative prognostic factors. Positive factors were diabetes and surgical treatment. In the present study, negative prognostic factors were alteration of consciousness and periorbital pain. According to the low number of deaths and the rarity of the disease, the 95% confidence intervals were broad.

The main limitation of this study is that it was retrospective; therefore, some information was unavailable, such as the degree of pain. Further prospective studies using a visual analog scale are needed to collect data on pain severity. This would allow for determination of which level of pain is associated with mortality. Moreover, the patients in our tertiary hospital may not represent the general population of patients with this disease because they were treated with antifungals or surgery before referral, affecting the pathological study or tissue culture results, and patients with more severe disease tended to be transferred to our tertiary hospital. Thus, selection bias seems inevitable.

In summary, the mortality rate of IFRS in this study was 23.1%. Negative prognostic factors were alteration of consciousness and periorbital pain. Clinicians must have a high index of suspicion for IFRS, and aggressive treatment should be considered. The low overall mortality rate in this study may be explained by early surgical intervention and early antifungal drug administration.

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REFERENCES

1. Turner JH, Soudry E, Nayak JV, Hwang PH. Survival outcomes in acute invasive fungal sinusitis: a systematic review and quantitative synthesis of published evidence. Laryngoscope. 2013;123:1112-8.
2. Soontrapa P, Larbcharoensub N, Luxameechanporn T, Cheewaruangroj W, Prakunhungsit S, Sathapatayavong B, et al. Fungal rhinosinusitis: a retrospective analysis of clinicopathologic features and treatment outcomes at Ramathibodi Hospital. Southeast Asian J Trop Med Public Health. 2010;41:442-49.
3. Gillespie MB, O'Malley BW Jr., Francis HW. An approach to fulminant invasive fungal rhinosinusitis in the immunocompromised host. Arch Otolaryngol Head Neck Surg. 1998;124:520-26.
4. Valera FC, do Lago T, Tamashiro E, Yassuda CC, Silveira F, Anselmo-Lima WT. Prognosis of acute invasive fungal rhinosinusitis related to underlying disease. Int J Infect Dis. 2011;15:e841-e844.
5. Kasapoglu F, Coskun H, Ozmen OA, Akalin H, Ener B. Acute invasive fungal rhinosinusitis: evaluation of 26 patients treated with endonasal or open surgical procedures. Otolaryngol Head Neck Surg. 2010;143:614-20.
6. DelGaudio JM, Clemson LA. An early detection protocol for invasive fungal sinusitis in neutropenic patients successfully reduces extent of disease at presentation and long term morbidity. Laryngoscope. 2009;119:180-83.
7. Chen CY, Sheng WH, Cheng A, Chen YC, Tsay W, Tang JL, Huang SY, et al. Invasive fungal sinusitis in patients with hematological malignancy: 15 years experience in a single university hospital in Taiwan. BMC Infect Dis. 2011;11:250.
8. Roongrotwattanasiri K, Fooanant S, Naksane L. Invasive fungal rhinosinusitis in Maharaj Nakorn Chiang Mai Hospital. J Med Assoc Thai. 2007;90:2524-8.
9. Piromchai P, Thanaviratananich S. Impact of treatment time on the survival of patients suffering from invasive fungal rhinosinusitis. Clin Med Insights Ear Nose Throat. 2014;7:31-34.
10. Zuniga MG, Turner JH. Treatment outcomes in acute invasive fungal rhinosinusitis. Curr Opin Otolaryngol Head Neck Surg. 2014;22:242-48.
11. Monroe MM, McLean M, Sautter N, Wax MK, Andersen PE, Smith TL, et al. Invasive fungal rhinosinusitis: a 15-year experience with 29 patients. Laryngoscope. 2013;123:1583-7.
12. Tarkan O, Karagün B, Ozdemir S, Tuncer U, Sürmelioğlu O, Cekiç E, et al. Endonasal treatment of acute invasive fungal rhinosinusitis in immunocompromised pediatric hematology-oncology patients. Int J Pediatr Otorhinolaryngol. 2012;76:1458-64.
13. Li Y, Li P, Zhang G. Diagnosis and endoscopic surgery of chronic invasive fungal rhinosinusitis. Am J Rhinol Allergy. 2009;23:622-25.
14. Suslu AE, Ogretmenoglu O, Suslu N, Yucel OT, Onerci TM. Acute invasive fungal rhinosinusitis: our experience with 19 patients. Eur Arch Otorhinolaryngol. 2009;266:77-82.
15. Lee DH, Yoon TM, Lee JK, Joo YE, Park KH, Lim SC. Invasive fungal sinusitis of the sphenoid sinus. Clin Exp Otorhinolaryngol. 2014;7:181-87.
16. Ilica AT, Mossa-Basha M, Maluf F, Izbudak I, Aygun N. Clinical and radiologic features of fungal diseases of the paranasal sinuses. J Comput Assist Tomogr. 2012;36:570-76.
17. Gillespie MB, Huchton DM, O'Malley BW. Role of middle turbinate biopsy in the diagnosis of fulminant invasive fungal rhinosinusitis. Laryngoscope. 2000;110:1832-6.
18. Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med. 2002;347:408-15.
19. Pemán J, Salavert M, Cantón E, Jarque I, Romá E, Zaragoza R, et al. Voriconazole in the management of nosocomial invasive fungal infections. Ther Clin Risk Manag. 2006;2:129-58.