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Case report

Chronic invasive sinus and intracerebral aspergillosis controlled by combination therapy with micafungin and a daily dose of 400 mg itraconazole oral solution

Taku Ogawa [a, *], Kana Matsumoto [c], Kazunori Tsujimoto [a], Naokuni Hishiya [a], Yutaka Yamada [a], Kenji Uno [a], Kei Kasahara [a], Koichi Maeda [a], Kazuhiko Nario [b], Keiichi Mikasa [a], Kunihiko Morita [c]

[a] Center for Infectious Diseases, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 634-8522, Japan
[b] Department of Otolaryngology-Head and Neck Surgery, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 634-8522, Japan
[c] Department of Clinical Pharmaceutics, Faculty of Pharmaceutical Sciences, Doshisha Women's College of Liberal Arts, Kodo, Kyotanabe, Kyoto, Japan

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ABSTRACT

Chronic invasive aspergillosis of the sinus is frequently fatal in the absence of early surgical and chemotherapeutic intervention because of its invasion of vascular tissue. We attempted to control a case of inoperable invasive aspergillosis of the sinus with micafungin and itraconazole oral solution. We prescribed a daily oral dose of 400 mg of itraconazole, which is twice the usual dose, and monitored the serum concentration of the drug. Finally, we were able to control the spread of the lesion. This case indicates that combination therapy with micafungin and a daily dose of 400 mg itraconazole oral solution is an alternative treatment strategy for inoperable invasive aspergillosis of the sinus.

1. Introduction

Although invasive aspergillosis of the sinus was believed to be a rare disease for years, an increasing number of cases have been recently reported. This disease occurs mostly in patients with mild immunodeficiency, such as diabetes mellitus [1]. A combination of radical surgical resection of the infected tissue and physical treatment with antifungal therapy is very important to treat these cases [2,3]. When invasive surgery is unendurable, the prognosis is reportedly poor [4]. Therefore, we believe that usual treatment with antifungal therapy would sometimes be futile. We attempted the administration of combination therapy with itraconazole oral solution with a daily dose of 400 mg and micafungin, while monitoring the serum concentration of itraconazole. Finally, we succeeded in controlling the progression of the lesion in this case.

2. Case report

A 74-year-old woman detected swelling and pain of a left buccal lesion. Because she had undergone a surgery for sinusitis of the left maxillary sinus 60 years before, she was prescribed clarithromycin by the local otolaryngology hospital, with the diagnosis of a post-operative maxillary cyst. Three months later, a soft tissue mass of approximately 4 cm in diameter was observed in her left maxillary sinus using plain magnetic resonance imaging (MRI) (Fig. 1). Because of suspicion of maxillary cancer, a paranasal mass biopsy was performed. Histological examination showed the presence of an Aspergillus-like filamentous fungus (Fig. 2) in the mucosal tissue obtained from the maxillary sinus. This fungus was identified as *Aspergillus fumigatus* on microbiological examination with slide culture technique. Radical surgery of the maxillary sinus was performed. Subsequently, oral voriconazole (VRCZ) was initiated as an antifungal therapy. After confirmation of an appropriate trough level, she was discharged from our hospital. We have continued to treat with oral VRCZ and found no deterioration.

One week before readmission to our hospital, approximately 1 year from the initiation of the treatment with VRCZ, she showed

* Corresponding author. 840 Shijo-cho, Kashihara-city, Nara-prefecture 634-8522, Japan. Tel.: +81 744 22 3051; fax: +81 744 24 9212.
E-mail addresses: t_ogawa@naramed-u.ac.jp, t.ogawammx@gmail.com (T. Ogawa).

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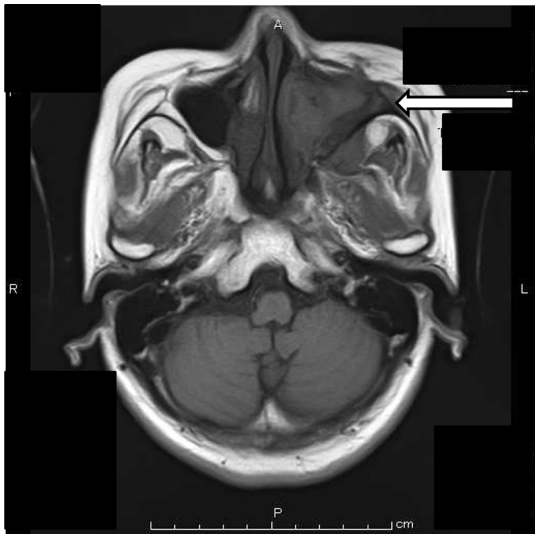

Fig. 1. There is some soft tissue mass pointed out in the left maxillary sinus.

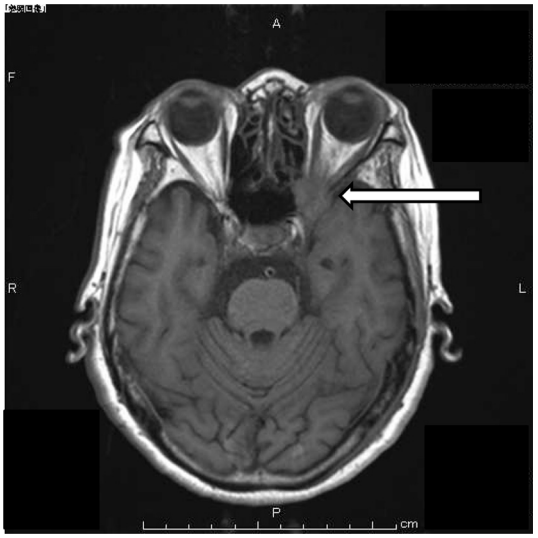

Fig. 3. Soft tissue image are seen in the left orbit on the 3rd admission day which may be the major cause of the orbital tip syndrome.

symptoms of disorientation, walking difficulty, and loss of vision in her left eye. MRI of the maxillary sinus revealed the rapid expansion of soft tissue toward the orbital apex. The cause of these symptoms was clearly not apparent histologically and microbiologically. However, the fact that her serum β-D-glucan also increased to 47.3 pg/mL led us to finally conclude that the expansion of the lesion was due to the recurrence of aspergillosis. She was admitted to our hospital immediately with a diagnosis of orbital apex syndrome (Fig. 3). Laboratory findings and a cerebrospinal fluid (CSF) test on a sample obtained by lumbar puncture at that time are summarized in Tables 1 and 2.

We began treating hyponatremia, which was quickly resolved within a few days. As treatment advanced, her consciousness improved. However, the blindness in her left eye did not improve. After a brain MRI examination, it became clear that the soft tissue mass had invaded the left frontal lobe of the brain. On the 8th day of admission, we started liposomal amphotericin B (L-AMB) at a dose of 4 mg/kg once per day. We continued L-AMB therapy for 14 days. Subsequently, because her general condition was fair, we added intravenous voriconazole (VRCZ) at a dose of 4 mg/kg twice daily to the L-AMB therapy. On the 31st day of admission, the trough concentration of VRCZ was 1.98 ng/mL; therefore, we decided to switch from intravenous administration to oral medication. At the same time, we terminated the L-AMB therapy. Because her AST, ALT, and γGTP levels increased gradually, we discontinued VRCZ on the 83rd day of admission. On the same day, we initiated a once daily 200 mg dose of oral itraconazole (ITCZ) solution as an alternative antifungal agent.

However, the soft tissue in the left maxillary sinus had gradually grown and invaded the left frontal lobe more extensively, as observed on MRI taken on the 89th day of admission. Therefore, a once daily 150 mg dose of micafungin (MCFG) was started on the 90th day of admission as a combination therapy with ITCZ. On the 92nd day of admission, we increased the dose of ITCZ to 200 mg twice daily. On the 97th day of admission, the dose of MCFG was increased to 300 mg once a day. We measured the serum concentration of ITCZ and hydroxyl-ITCZ after increasing the dose of ITCZ, using high-performance liquid chromatography (HPLC). On the

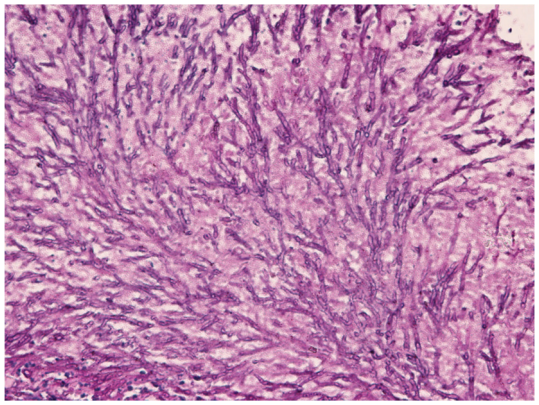

Fig. 2. Aspergillus-like filamentous fungus is seen in the tissue obtained by maxillary sinus mucosal biopsy (PAS stain, ×1000).

Table 1
Laboratory findings on the admission day.

WBC	7800/μL	TP	6.7/dL	β-D glucan	6.7 pg/ml
neutro	84.5%	ALB	3.6 g/dL	PCT	0.05 ng/ml
baso	1%	AST	25 U/L	Aspergillus Ag	0.0
eosino	0.2%	ALT	14 U/L	HbA1C(JDS)	5.9%
mono	6.7%	γ-GTP	22 U/L		
lymph	7.6%	BUN	17.0 mg/dL	PT	98%
RBC	427 × 104/μL	Creat	0.47 mg/dL	PT-INR	1.01
HCT	34.8%	Na	118 mEq/L	APTT	33.1 Sec
HGB	12.0 g/dL	K	3.3 mEq/L	Fbg	540 mg/dL
PLT	36.8 × 104/μL	Cl	80 mEq/L	D-dimer	0.7 μg/ml
ESR	67 mm/h	Glu	119 mg/dL		
		CRP	1.1 mg/dL		

Table 2
Laboratory data from spinal fluid on the admission day.

Pressure	Not measured	Cryptococcal antigen	Negative
Color	Clear	India ink capsule stain	Negative
Cell count	2/3 μL	Mycology culture	Negative
Nt	1/3 μL	Bacterial culture	Negative
TP	31 mg/dL	PCR for tuberclosis	Negative
Glu	67 mg/dL	Culture for mycobacteria	Negative
Cl	102 mEq/L	Ziehl-Neelsen stain	Negative
ADA	≦1.0 U/L		
RPR	Negative		
FTA-ABS	Negative		