Successful treatment with voriconazole combined with amphotericin B-liposome for fluconazole-resistant pulmonary cryptococcosis after renal transplantation

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Abstract

Cryptococcosis is an invasive fungal infection that is common among organ transplant recipients, and it is challenging to treat among these patients because of their immunocompromised status. Fluconazole (FLCZ) is recommended as a first-line treatment modality for pulmonary cryptococcosis in organ transplant recipients. However, cases of FLCZ resistance among *Cryptococcus neoformans* isolates have been reported from the Asia Pacific region. Previous studies have reported the efficacy of voriconazole (VRCZ) in patients with FLCZ-resistant fungal infections. Herein, we report a case of FLCZ-resistant pulmonary cryptococcosis after renal transplantation that was successfully treated with VRCZ combined with amphotericin B-liposome (L-AMB). The patient was a 23-year-old woman who underwent living-donor kidney transplantation at age 20 years. She has attended our hospital since before for mental retardation, epilepsy, and dilated cardiomyopathy. At age 23 years, she presented to our hospital with fever and cough. She was diagnosed with pulmonary cryptococcosis based on positive-serum cryptococcal antigen. Chest radiography showed bilateral consolidations. Fosfluconazole (F-FLCZ) was administered, and her condition improved. However, she developed cough and fever again on day 60 of hospitalization. Cryptococcosis recurrence was suspected due to the high degree of cryptococcal antigen titers showed (1:2048) taken on the same day. Therefore, L-AMB was added, and F-FLCZ was substituted with VRCZ. Her condition improved, but L-AMB was discontinued due to hyponatremia, hypokalemia, and elevated serum creatinine. This indicates that VRCZ caused the remission. She was discharged after 6 months of admission. In conclusion, this case shows the efficacy of VRCZ combined with L-AMB for refractory pulmonary cryptococcosis.

Keywords Cryptococcosis · Fluconazole resistant · Renal transplantation · Voriconazole

Introduction

Cryptococcosis is an important opportunistic infection in organ transplant recipients, and these patients are difficult to treat because of their immunocompromised status. Fluconazole (FLCZ) is recommended as first-line therapy for pulmonary cryptococcosis in organ transplant recipients [1].

However, FLCZ-resistance among *Cryptococcus neoformans* (*C. neoformans*) isolates have been reported from Asia Pacific region [2]. Meanwhile, previous studies have shown that voriconazole (VRCZ) is effective for FLCZ-resistant fungal infections [3, 4]. Herein, we report a case of successful treatment with VRCZ and amphotericin B-liposome (L-AMB) for FLCZ-resistant pulmonary cryptococcosis after renal transplantation.

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Case report

A 23-year-old woman with a past history of mental retardation, epilepsy, and dilated cardiomyopathy underwent renal transplantation at age 20 years due to renal failure caused by lymphadenitis. Immunosuppressive agents including

methylprednisolone, mycophenolate mofetil, and tacrolimus were administered. At age 23 years, she presented to our hospital with fever and cough. Vital signs were normal on admission, and her respiratory sounds were clear. Although she looked pale, she was alert and responsive. Blood examination showed elevated white blood cell counts ($18,300/\text{mm}^3$) and C-reactive protein (CRP) (15.65 mg/dl) (Table 1). Chest radiography showed bilateral consolidations, and chest computed tomography (CT) revealed plural consolidations at the peripheral side of the lung (Fig. 1a, b). Cefotaxime was initially administered, but it did not improve the patient's condition. Further investigations were conducted, and serum

cryptococcal antigen test showed positive results. Cytomegalovirus antigenemia assay, β -D-glucan, and T-SPOT. TB assay were negative. Therefore, she was diagnosed with pulmonary cryptococcosis. Cerebrospinal fluid (CSF) test was normal; thus, cryptococcal meningitis was ruled out. Fosfluconazole (F-FLCZ) 200 mg/day was administered; her condition temporally improved, and chest radiography and CT showed regression of consolidations (Fig. 1c, d). However, on day 60 of admission, she developed fever and cough again, and serum CRP level was also increased again (Fig. 2). Chest radiography and CT revealed aggravation of consolidations (Fig. 1e, f). Recurrence of pulmonary cryptococcosis was suspected, because cryptococcal antigen titer was markedly high degree at 1:2048. Amphotericin B-liposome (L-AMB) 150 mg/day was added, and F-FLCZ was switched to VRCZ 350 mg/day. Although her condition and serum CRP level were improved, it became difficult to continue the L-AMB because it caused hyponatremia, hypokalemia and elevation of serum creatinine. Thus, it was discontinued at 7 weeks, and only VRCZ was administered. Thereafter, she maintained remission, and cryptococcal antigen titer decreased gradually. Her serum creatinine level gradually decreased, on the other hand, hyponatremia and hypokalemia persisted after the withdrawal of L-AMB. She was discharged at 6 months from admission, and her serum cryptococcal antigen titer decreased to 1:256 at the time of discharge. VRCZ has since been administered on outpatient basis, and there has been no recurrence to date. After 6 months from discharge, her cryptococcal antigen titer decreased to 1:64.

Table 1 Laboratory findings on admission

Hematology	
WBC	18,300 / μl
NEUTRO	14,713 / μl
LYMPHO	2342 / μl
RBC	399×10^4 / μl
Hb	12.3 g/dl
PLT	25.0×10^4 / μl
Biochemistry	
AST	17 U/l
ALT	8 U/l
T-Bil	1.1 mg/dl
LDH	209 U/l
TP	7.2 g/dl
ALB	4.2 g/dl
BUN	18 mg/dl
Cr	1.13 mg/dl
UA	7.4 mg/dl
Na	139 mEq/l
K	3.5 mEq/l
Cl	99 mEq/l
CRP	15.65 mg/dl
IgG	693 mg/dl
Serology	
β -D glucan	< 6.0 pg/ml
<i>Aspergillus</i> Ag	Negative
Cytomegalovirus antigenemia	Negative
T-SPOT	Negative
<i>Mycoplasma Pneumoniae</i> IgM	Negative
Cryptococcal antigen	Positive
Cerebrospinal fluid test	
WBC	< 1 / μl
Protein	32 mg/dl
Glucose	52 mg/dl
Chloride	119 mEq/l
Cryptococcal antigen	Negative
India ink capsule stain	Negative
Culture	Negative

Discussion

The Infectious Diseases Society of America (IDSA) guidelines, recommended FLCZ as a first-line therapy for pulmonary cryptococcosis in organ transplant recipients [1]. In the current case, although F-FLCZ was initially effective temporarily, it did not prevent recurrence. There are two possibilities for the cause of treatment failure with F-FLCZ. First, *C. neoformans* might have developed resistance against FLCZ in this patient. The incidence of FLCZ resistance among *C. neoformans* isolates range from 5.1 to 22.6% in the Asia Pacific region [2]. Bacterial culture was not available in the current patient, because it was difficult to conduct a bronchoscope test due to her mental retardation. Although the minimum inhibitory concentration (MIC) of FLCZ against *C. neoformans* is unknown, the MIC might be high according to the clinical course. Second, blood concentration of FLCZ might not be fully elevated. FLCZ is primarily eliminated through the urine by the kidney; thus, it is recommended that dose of FLCZ be decreased in patients with renal impairment [5]. Because the estimated glomerular

Fig. 1 Chest radiography and chest CT findings. **a** Chest radiography showed bilateral consolidations on admission. **b** Chest CT revealed plural consolidations at the peripheral side of the lung on admission.

c, d Chest radiography and CT showed regression of consolidations after F-FLCZ administration. **e, f** Chest radiography and CT revealed aggravation of consolidations on day 60 of admission

filtration rate was approximately 30–50 ml/min/m² in this patient, a half normal dose of F-FLCZ for adults was administered. However, it might be that the drug concentration was not increased enough to the effective level. Previous studies have reported that FLCZ clearance is more rapid in children than that in adults, because children have a larger volume of distribution and faster elimination rate than adults [6]. Although the patient was not a child but a young adult, her FLCZ clearance might be more rapid than that of older adults according to above studies. Moreover, her height was 130 cm, and she weighed 32 kg, which was equal to that of a typical 9-year-old-girl. Thus, it is likely that her volume of distribution was larger than that of an adult. According to the above considerations, it was presumed that the pharmacokinetics of FLCZ in this patient was similar to that in children. In this case, the volume distribution and blood concentration

of FLCZ were unknown. Additionally, the volume of distribution of agents is related to the water volume; however, there are no studies that mention why the distribution of FLCZ in children is larger than that in adults. Therefore, our consideration is only speculative, and the reason behind the treatment failure with F-FLCZ is unclear.

Voriconazole was effective for cryptococcosis in our case. The IDSA guidelines recommend VRCZ as salvage therapy for cryptococcosis [1]. Similar with FLCZ, VRCZ is also a triazole antifungal agent, Hui-Hua et al. reported a case of FLCZ-resistant cryptococcal meningitis successfully treated with VRCZ [4]. One study reported that a high percentage of FLCZ-resistant *C. neoformans* was susceptible to VRCZ in vitro [7]. These reports suggest that VRCZ is highly effective for FLCZ-resistant cryptococcosis. In addition, VRCZ is metabolized by the liver;

Fig. 2 Clinical course

thus, it is useful for renal impairment. However, VRCZ may also lead to adverse events such as liver dysfunction and vision problems. As such, therapeutic drug monitoring is recommended in VRCZ administration. Frequent monitoring would lead to appropriate serum concentration of VRCZ, which prevents not only adverse effect but also treatment failure due to low serum concentration.

L-AMB is a polyene antifungal agent, which is recommended as a first-line therapy for central nervous system cryptococcosis by IDSA guidelines [1]. However, because of the risk of nephrotoxicity, L-AMB should be used with caution in transplant recipients and is not recommended as first-line therapy [1]. In our case, L-AMB combined with VRCZ lead to remission; thus, L-AMB was also effective. However, the patient suffered from adverse effects of L-AMB, such as renal injury and electrolyte imbalances. Serum creatinine level was decreased slowly after the discontinuance of L-AMB, but it has not recovered on the basis so far. Furthermore, the patient had to need supplementary of sodium chloride and potassium chloride for several weeks after the withdrawal of L-AMB. L-AMB

should be used carefully despite efficacy for cryptococcosis in renal transplant recipient.

Triazole agents, such as FLCZ and VRCZ, have good antifungal activities, but also have drug interactions because of potent inhibition of the P450 enzyme system. Interactions with immunosuppressive agents, especially calcineurin inhibitors, are of concern in post-transplantation patients. When F-FLCZ administration was initiated, tacrolimus dosage was reduced by three-fourth. However, the serum tacrolimus trough level was elevated, and tacrolimus dosage was finally reduced by one-seventh (Fig. 2).

It is reported that cryptococcal antigen is correlated with disease activity. However, studies about cryptococcal antigen titer are limited, Dohtsu et al. reported sixteen cases of pulmonary cryptococcosis in which serum cryptococcal antigen titer was clinically evaluated [8]. In this report, 4 patients were negative for the cryptococcal antigen, and only 2 patients had cryptococcal antigen titer of more than 1:256. Another study reported that a serum cryptococcal antigen titer of more than 1:64 was independently associated with an increased risk of central nervous system (CNS) diseases

[9]. In our case, cryptococcal antigen titer was not tested before start of therapy, but her cryptococcal antigen titer was one of the highest in the cases of pulmonary cryptococcosis previously reported. The current case was refractory cryptococcosis, and T cell dysfunction was mainly involved with pathophysiology. However, it seems that nothing of CNS involvement despite refractory cryptococcosis led to good outcome in our case.

In summary, VRCZ combined with L-AMB was effective for refractory pulmonary cryptococcosis in a kidney transplant recipient. Particularly, VRCZ should be considered as first-line therapy for pulmonary cryptococcosis in young patients with renal impairment.

Compliance with ethical standards

Conflict of interest All the authors have declared no competing interest.

Human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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