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Case report

Voriconazole as a secondary prophylaxis for cryptococcal meningitis during hematopoietic stem cell transplantation

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ABSTRACT

Antifungal prophylaxis is crucial for successful hematopoietic stem cell transplantation (HSCT). Maintenance therapy with fluconazole (FLCZ) is generally prescribed as secondary prophylaxis in patients with human immunodeficiency virus infection and non-immunocompromised hosts. However, previous reports have revealed that FLCZ is insufficient as a secondary prophylaxis for cryptococcal infection in HSCT cases. There is no well-established evidence of effective secondary prophylaxis against cryptococcal infection in conditions of severe immunosuppression, such as in HSCT. Herein, we report a case of atypical chronic myeloid leukemia (aCML) presenting with cryptococcal meningitis. A 58-year-old man with progressive leukocytosis and headache was referred to our hospital. Bone marrow biopsy revealed aCML. Because the estimated overall survival was limited, HSCT was indicated. Furthermore, enhanced magnetic resonance imaging and lumbar puncture aided in diagnosing cryptococcal meningitis, which was treated with a combination therapy comprising liposomal amphotericin B and 5-fluorocystine for 28 days. Given the high recurrence rate of cryptococcal meningitis, voriconazole (VRCZ) dose was calculated using the trough concentration of VRCZ in the cerebrospinal fluid. Eventually, HSCT was successfully performed at an appropriate therapeutic range of VRCZ. To the best of our knowledge, there is no case report on HSCT with secondary prophylaxis against cryptococcal meningitis. Our report thus emphasizes the efficacy of VRCZ maintenance therapy as secondary prophylaxis for cryptococcal infection.

Introduction

Antifungal therapy during hematopoietic stem cell transplantation (HSCT) is crucial because fungal infection is a potentially lethal complication [1–3]. Cryptococcal infection during HSCT, particularly cryptococcal meningitis, has been reported previously, with a mortality rate of approximately 50 % [4]. Unlike aspergillus and candida infections [5–7], few established prophylactic strategies are available for cryptococcal infection in patients undergoing HSCT. We encountered a case with cryptococcal meningitis prior to HSCT. Our patient underwent allogeneic HSCT without recurrence of cryptococcal meningitis with secondary prophylactic voriconazole (VRCZ).

Case report

A 58-year-old man was admitted to our hospital owing to progressive malaise and headache. His medical history and family history were unremarkable, and he was not taking any medication. He is a current smoker and smokes a pack of cigarettes a day. He denied any history of alcohol consumption or illicit drug use or recent history of travel.

Physical examination on admission revealed enlargement of small lymph nodes around the anterior region of the neck (up to 10 mm diameter). Petechiae on the upper limbs and a purpuric lesion on the lower limbs were observed. Laboratory studies revealed a white blood cell count of 28,600/μL (blast; 6.0 %), hemoglobin of 12.2 g/dL, platelet count of 18,000/μL, and a negative result for human immunodeficiency virus (HIV) infection (Table 1). Bone marrow specimen showed dysplasia of megakaryocytes and granulocyte lineage cells. G-banding examination revealed nomal karyotype. Furthermore, cytogenetic analysis showed negative

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Table 1
Laboratory test at admission.

【Peripheral blood】		【Biochemistry】	
WBC	28,600 /μL	TP	8.6 g/dL
Neu	59.0 %	Alb	4.7 g/dL
Lym	8.0 %	AST	68 IU/L
Mo	0.0 %	ALT	93 IU/L
Eo	1.0 %	LDH	824 IU/L
Ba	0.0 %	T-Bil	1.6 mg/dL
Blast	4.0 %	D-Bil	0.1 mg/dL
Myel	23.0 %	Amy	77 IU/L
Meta	2.0 %	Glu	115 mg/dL
RBC	380 × 10^4 /μL	BUN	19.5 mg/dL
Hb	12.2 g /dL	Cre	1.14 mg/dL
MCV	98 fl	UA	5.6 mg/dL
Plt	18 × 10^9 /L	Na	127 mEq/L
【Coagulation】		K	4.6 mEq/L
PT	70 %	Cl	91 mEq/L
APTT	31.1 s	CRP	1.72 mg/dL
FDP	10.2 mg/mL	Procalcitonin	0.13 ng/mL
Fib	532	Haptoglobin	243 mg/dL
AT3	101 %	VitB12	1170 pg/mL
		Zinc	120 μg/dL
		Mg	2.2 mg/dL
		NAP score	48

findings for *BCR/ABL*, *JAK2* V617 F mutation, and *CSF3R* mutation. He was diagnosed with atypical chronic myeloid leukemia (aCML) via bone marrow biopsy.

Magnetic resonance imaging (MRI) was performed to investigate the patient's headache. MRI with gadolinium-contrast showed hyperintensity in the cerebral cortex (Fig. 1, arrowheads). Lumbar puncture revealed invasion of mature lymphocytes in CSF. Further analysis of cerebrospinal fluid (CSF) revealed positive for cryptococcal antigen (Table 2). Consequently, he was diagnosed with cryptococcal meningitis.

Table 2
Laboratory test of cerebrospinal fluid.

pH (CSF)	7.4
cell count (CSF)	852 /3 mL
glucose (CSF)	60 mg/dL
glucose (plasma)	112 mg/dL
total protein (CSF)	156 mg/dL
PCR (mycobacterium)	Negative
Cryptococcal antigen (CSF)	x2
Cryptococcal antigen (serum)	x2

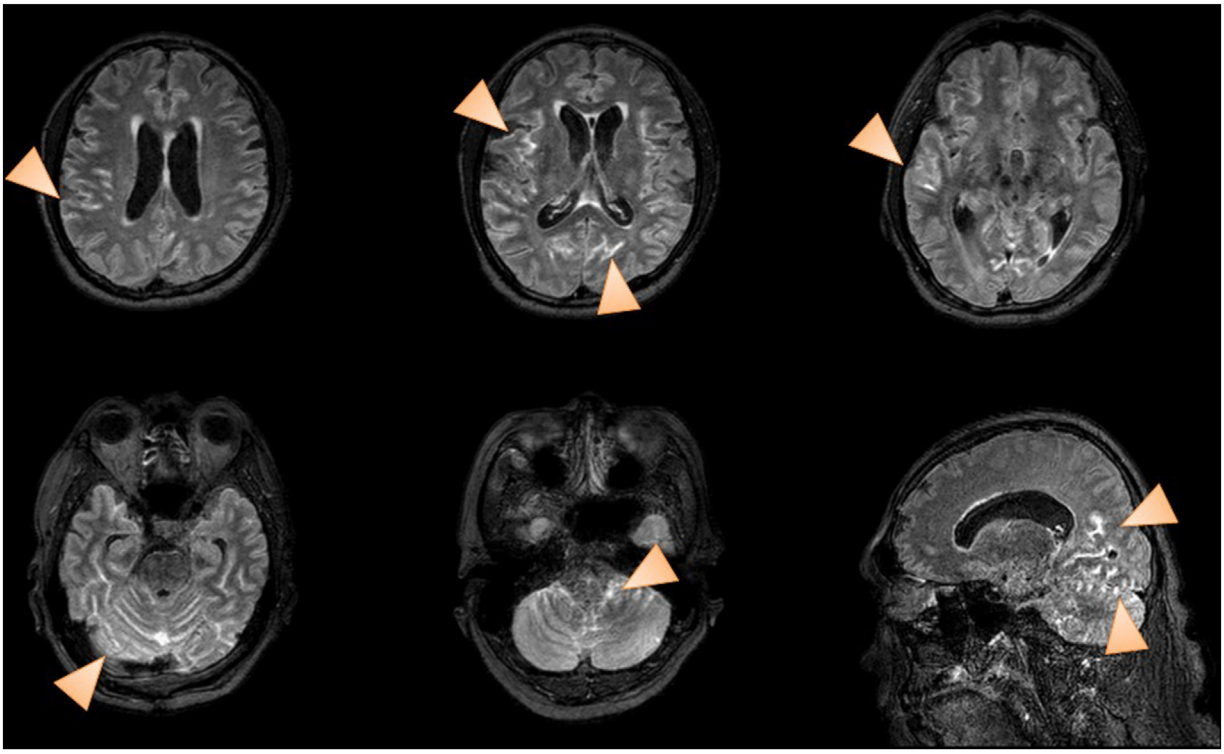

Fig. 1. Gadolinium-contrast magnetic resonance imaging (MRI) of the head.
Gadolinium-enhanced MRI revealed high intensity in the cerebral cortex (arrowheads).

We started the patient on liposomal amphotericin B (6.0 mg/kg/day) and flucytosine (25 mg/kg/day). Because the subsequent FLCZ monotherapy induced kidney injury, VRCZ at 600 mg/day was initiated as consolidation therapy. According to local antibiogram data, cryptococcal isolates showed VRCZ-minimum inhibitory concentration (MIC) of <0.04 μg/mL. VRCZ levels in the plasma and CSF were 1.01–1.51 μg/mL and 1.28–2.3 μg/mL, respectively. The transfer rate of VRCZ to the CSF was reported to range from 22 % to 100 % (median 46 %) [11], and the rates in our case were sufficient (approximately 65.0 %). Trough concentration of VRCZ in CSF was higher than previously reported local antibiogram MIC [8,9] as well as global reports [10,11]. We confirmed that VRCZ concentration in the CSF exceeded the MIC.

After 2 months of maintenance therapy, an unrelated HSCT for aCML was planned. The donor was a human leukocyte antigen match (serological 8/8, allele 8/8) and an ABO mismatch from the Japan Marrow Donor Program. The HSCT regimen constituted fludarabine and busulfan, whereas the graft-versus-host disease (GVHD) prophylaxis regimen comprised methotrexate and tacrolimus. To ensure a reasonable assurance of marrow recovery post HSCT, a dose of 1.18×10^6 $CD34^+$ cells/kg was prepared. Engraftment of granulocyte stem cells in the patient was successful on day 22. Although he developed GVHD that manifested as a grade 2 skin rash, the HSCT was successful without the recurrence of cryptococcal meningitis. He survived for more than 5 years after HSCT.

Discussion

The morbidity and mortality rates of fungal infections in HSCT have significantly decreased owing to the recent progress in antifungal therapy [4]. Cryptococcal meningitis is a rare HSCT-related complication, and there have been only few reported cases. According to a report by Firacative et al., cryptococcal infection could develop within 5 years after HSCT, and approximately half (52 %) of the cases of cryptococcal infection developed meningitis [4]. The authors pointed that a quarter of the cases (6 of 22 cases) developed cryptococcal infection or meningitis despite FLCZ prophylaxis. In patients with HIV, FLCZ prophylaxis has been reported as an insufficient prophylactic strategy against cryptococcal infection [12]. These findings suggest that FLCZ prophylaxis is potentially inadequate during HSCT. In the last decade, the use of VRCZ as secondary prophylaxis for invasive fungal infection in HSCT has been reported [5,7]. These reports, however, did not include cryptococcal infection. Given the higher CSF transfer rate, VRCZ is considered suitable for post-cryptococcal meningitis prophylaxis regimen.

Almost half of the cases of cryptococcal meningitis relapse without secondary prophylaxis are in patients with HIV [13]. Despite the high recurrence risk, we performed HSCT considering the poor prognosis of aCML (estimated overall survival was approximately 12 months) [14–16]. Considering the immunosuppression period of HSCT, we maintained the VRCZ trough concentration over cryptococcal MIC. Our case showed similar estimated CSF transfer rate of VRCZ (22 %–100 %) [17]. We continued the VRCZ for >3 months after HSCT according to the data on immune reconstitution period. Our results show that HSCT was successfully performed without cryptococcal meningitis recurrence.

In summary, we encountered a case of aCML and demonstrated the safety and efficacy of VRCZ as secondary antifungal prophylaxis in cryptococcal meningitis treatment by appropriately monitoring VRCZ levels in plasma and CSF.

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None.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Ethical approval

Our manuscript was approved by suzuka general hospital ethical committee.

Author contribution

KN was responsible for the manuscript. EK, KN, KI, YS, AF and KK treated this patient. IS was the chief investigator and supervised the manuscript.

Declaration of Competing Interest

The authors declare no conflicts of interest associated with this manuscript.

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