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Case Report

Cryptococcal meningitis following umbilical cord blood transplantation, association between the occurrence of cryptococcal infection and tacrolimus discontinuation among allogeneic hematopoietic stem cell recipients☆

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ABSTRACT

Few cases of cryptococcal infection following umbilical cord blood transplantation (UCBT) have been reported. We report a case, where cryptococcal infection occurred soon after rapidly reducing the dose of tacrolimus in a UCBT recipient who received micafungin prophylaxis during the early phase of transplantation. The etiology of cryptococcal infection following allogeneic hematopoietic stem cell transplantation (allo-HSCT), including UCBT, might be associated with rapid dose-reduction of calcineurin inhibitors, such as tacrolimus during early phase of allo-HSCT. To our knowledge, this is the first English-language report to describe in detail a case of cryptococcal meningitis with fungemia during early phase of UCBT.

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1. Introduction

Recipients of allogeneic hematopoietic stem cell transplantation (allo-HSCT) are at high risk of invasive fungal infections but rarely develop cryptococcosis [1]. However, only three cases of cryptococcal infection following umbilical cord blood transplantation (UCBT) have been reported in the literature that focused on infection of the central nerve system following UCBT to date [2,3]. The reason cryptococcal infection is extremely rare in allo-HSCT recipients, including UCBT, remains uncertain [4]. This case report describes cryptococcal meningitis with fungemia that occurred soon after rapidly reducing the dose of tacrolimus in a recipient of UCBT who received micafungin prophylaxis during the early phase of transplantation. Calcineurin inhibitors, including tacrolimus, have been reported to affect growth of fungi, including *Cryptococcus neoformans* [5,6]. Therefore, we hypothesized that tacrolimus discontinuation could be a risk factors for cryptococcal infection in allo-HSCT recipients.

2. Case report

A 55-year-old man was diagnosed with follicular lymphoma in 2000 and underwent radiation treatment and CHOP (cyclophosphamide, adriamycin, vincristine, and prednisone) chemotherapy. Relapse was observed in 2013. Despite undergoing salvage chemotherapy followed by radiation treatment, a sudden increase in size of abdominal tumors was observed in July 2014. The

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patient's diagnosis was considered to have transformed into diffuse large B-cell lymphoma. The tumors showed a tendency to increase with salvage chemotherapy in addition to the presence of urinary retention due to displacement of the ureter. Therefore, UCBT was performed in April 2015. The transfused nuclear cell count was 2.10×10^7/kg, and the CD34-positive cell count was 1.29×10^5/kg. In total, 180 mg/m^2 of fludarabine, 80 mg/m^2 of melphalan, and 12.8 mg/kg of busulfan were administered by intravenous injection as pretreatment. To prevent graft-versus-host disease (GVHD), 0.025 mg/kg of tacrolimus and 20 mg/kg of mycophenolate mofetil were administered by infusion and orally, respectively the day before the transplant. His HIV antibody was negative. Antifungal prophylaxis was initiated with 150 mg of micafungin from 8 days prior to the transplant. The prophylactic regimen (150 mg of micafungin) had been used as an anti-mold prophylaxis in some patients in a clinical trial that was approved by the Institutional Review Board of Toranomon Hospital. Engraftment of neutrophils was achieved on the 13th day post-transplantation. Acute Grade II GVHD (stage: skin 1, liver 0, and gut 1) appeared on the 14th day post-transplantation, but steroid therapy was not given because of spontaneous remission. The patient developed fever (body temperature 38 °C) from the 20th day post-transplantation, and the condition persisted thereafter. An approximately 5-cm diameter tumorous lesion was identified in the lower lobe of the right lung on computed tomography (CT) scan of the chest on the 34th day post-transplantation. Transbronchial lung biopsy was performed on the 40th day post-transplantation, and pathological examination revealed a diagnosis of recurrent lymphoma. However, there was no pathological and microbiological evidence of invasive fungal infection in the lung fields. Consequently, the presence of a graft-versus-lymphoma (GVL) effect was anticipated; therefore, the dose of tacrolimus was reduced rapidly from the 43rd day post-transplantation, and the drug was discontinued on the 47th day.

Yeast was detected from blood culture obtained for persistent fever on the 47th day post-transplantation on 51st day (Fig. 1) although yeast was not detected from blood cultures obtained on the 42nd day and 44th day. On the 51st day, the 150-mg dose of micafungin was changed to 3 mg/kg of liposomal amphotericin B. The yeast was identified as *Cryptococcus* spp. on the 52nd day after the transplant. No meningeal irritation was identified, but mild headache and disorientation appeared from the 53rd day post-transplantation. Therefore, cerebrospinal fluid (CSF) analysis was performed at the 54th day post-transplantation. Lumbar puncture yielded clear CSF with 2 cells/μL. CSF glucose and protein were normal, at 86 mg/dL and 19 mg/dL, respectively; cryptococcal antigen was positive (titer of 1:8). CSF Gram staining did not show any microorganisms. India ink smear revealed no yeast cells. Subsequently, 3000 mg of flucytosine was added to liposomal amphotericin B on the same day. In addition, serology was positive for cryptococcal antigens (titer of 1:16) on the 56th day post-transplantation. *Cryptococcus* spp. was identified from the cerebrospinal fluid culture on the 59th day. Thus, he was diagnosed as cryptococcal meningitis with fungemia.

Drug susceptibility of the strain was as follows: Amphotericin B 1μg/mL (MIC, minimum inhibitory concentration), 5-Flucytosine 2μg/mL (IC_{50}, 50% inhibitory concentration), Fluconazole 2–4μg/mL (IC_{50}), Itraconazole 0.12μg/mL (IC_{50}), and Voriconazole 0.03μg/mL (IC_{50})). Furthermore, the Cryptococcal strain was identified as *C. neoformans* by support of sequencing of the internal transcribed spacer (ITS) region, D1/D2 region, and intergenic spacer (IGS) region of the ribosomal RNA gene of the isolated yeast [7–9].

Initiating the concomitant use of liposomal amphotericin B (3 mg/kg) and flucytosine (3000 mg/day) on the 54th day post-transplantation, blood culture became negative immediately on the 56th day; headache and disorientation improved from the 60th day. Blood culture and cerebrospinal fluid analysis findings on the 83rd day post-transplantation were negative; hence, the antifungal combination regimen was changed to intravenous fosfluconazole (400 mg/day) on the 88th day. No recurrence of cryptococcal infection was observed during the therapeutic duration.

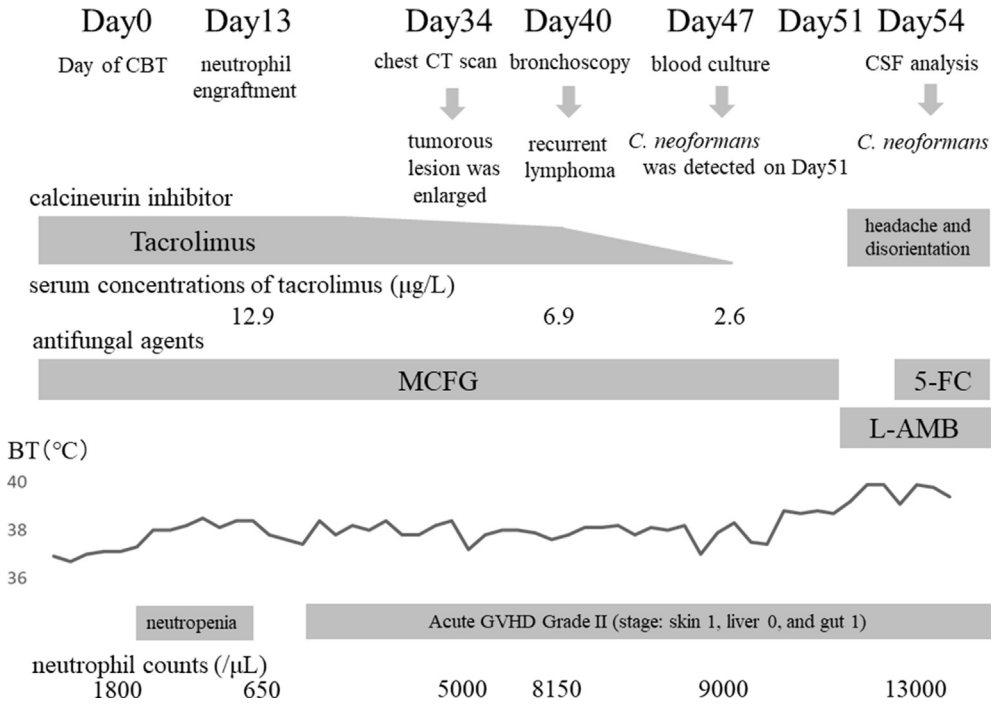

Fig. 1. Clinical course of the patient with disseminated cryptococcosis. *C. neoformans*, *Cryptococcus neoformans*; CBT, cord blood transplantation; CSF, cerebrospinal fluid; CT, computed tomography; BT, body temperature; MCFG, micafungin; 5-FC, flucytosine; L-AMB, liposomal amphotericin B.

Table 1
Literature review of cases diagnoses with cryptococcosis after allogeneic hematopoietic stem cell transplantation.

	Age/ Gender	Underlying condition	Transplant Source	Conditioning Regimen	Date of onset	Focus of infection	Antifungal prophylaxis	Cryptococcal species	Treatment	Reference No
1	31/Male	ALL	uCBT	Flu, Mel	(NA)	cryptococcemia	(NA)	*C.neoformans*	L-Amb+5FC	[2]
2	12/Female	LBL	allo BMT	TBI, TESPA, CY	Day 64	cryptococcemia	FLCZ	(NA)	AmBd+5FC	[13]
3	40/Female	AML	allo PBSCT	CY, Flu, (+ATG)	Day 2	meningitis	ITCZ	*C. adelinesis*	L-Amb+5FC	[14]
4	(NA)	(NA)	uCBT	(NA)	Day 50	meningitis	(NA)	(NA)	(NA)	[3]
5	(NA)	(NA)	uCBT	(NA)	Day 538	meningitis	(NA)	(NA)	(NA)	[3]
6	55/Male	FL transformation	uCBT	Flu, Mel, iBu	Day 54	meningitis	MCFG	*C.neoformans*	L-Amb+5FC	current report

The date of onset means that the day when cryptococcosis occurred firstly from the day of transplantation (Day 0).
NA, not available; LBL, lymphoblastic lymphoma; AML, acute myeloid leukemia; FL, follicular lymphoma; allo BMT, allogeneic bone marrow transplantation; allo PBSCT, allogeneic peripheral blood stem cell transplantation; uCBT, umbilical cord blood transplantation; TBI, total body irradiation; TESPA, thiotepa; CY, cyclophosphamide; Flu, fludarabin phosphate; ATG, anti-thymocyte globulin; Mel, melphalan; iBu, intravenous busulfan; FLCZ, fluconazole; ITCZ, itraconazole; MCFG, micafungin; AmBd, amphotericin B deoxycholate; 5FC, flucytosine; L-Amb, liposomal amphotericin B.

3. Discussion

Cryptococcal infection is extremely rare among allo-HSCT recipients [4]. To our knowledge, only 6 cases of cryptococcal infection following allo-HSCT, including the present case (Table 1) have been reported to date [2–4]. Among the 6 cases, 4 were recipients of UCBT [2,3]. Cryptococcal infection is one of the common fungal infections among solid organ transplant (SOT) recipients [4], but the reason it is extremely rare in allo-HSCT recipients remains uncertain. Widespread use of fluconazole prophylaxis which has activity against *Cryptococcus* for allo-HSCT recipients may be associated with the lower incidence of cryptococcosis in allo-HSCT settings than in SOT settings [4]. The present case is the first and only case of the cryptococcal infection among 447 recipients of UCBT who received micafungin prophylaxis on the day of transplantation (Day 0) between December 2008 and December 2016 at our institute (0.22%). The incidence of cryptococcal infection in patients who underwent SOT was reported to be between 0.3% and 5% [4]. It is estimated to still be higher than that in UCBT recipients who received micafungin prophylaxis at our institute (0.22%) although micafungin does not have anti-cryptococcal activity. This result probably indicates that widespread use of fluconazole prophylaxis is not the only reason cryptococcal infection is extremely rare in allo-HSCT recipients.

Cryptococcal species live ubiquitously in the environment, and its spores colonize the alveolar space in the human lung [10]. Based on a dissemination model of *Cryptococcus neoformans*, in immunocompetent individuals, activated macrophage phagocytose and surround Cryptococci to form granulomas. Cryptococci in granulomas is thought to remain latent or be reactivated but can cause disseminated infection once the host immune status changes [10]. In the present case, cryptococcal infection occurred soon after rapidly reducing the dose of tacrolimus during the early phase of transplantation. This rapid reduction during the early phase is not common practice at our institute. However, it was needed in the present case to induce the GVL for treating the recurrence of lymphoma. Calcineurin inhibitors, such as tacrolimus and cyclosporine affect calcineurin-mediated signaling pathways and provide a stress response to fungus by inhibiting a protein required for fungal growth related to its virulence [5,6]. In a previous clinical study regarding *C. neoformans* infection of SOT recipients, the 90-day survival rate of recipients who received both antifungal agent and calcineurin inhibitors (91%) was higher than that of those who received antifungal agent alone (61.5%) significantly ($P = 0.02$) [11]. According to these results, calcineurin inhibitors can inhibit growth and virulence of fungi, including *Cryptococcus*. In addition, echinocandins, including micafungin might have anti-cryptococcal activity when administered with tacrolimus simultaneously because anti-cryptococcal activity has been demonstrated by the combination of tacrolimus and caspofungin, which is an echinocandin other than micafungin *in vitro* [12]. These previous studies suggested that rapid discontinuation of calcineurin inhibitors might enhance virulence of latent *C. neoformans* and inhibit the anti-cryptococcal activity of the combination of micafungin and tacrolimus. This might have led to reactivation and subsequent dissemination of *C. neoformans* during the early phase of transplantation when immune function of the present patient was severely suppressed.

In conclusion, discontinuation of calcineurin inhibitors, such as tacrolimus might be associated with the etiology of cryptococcal infection following allo-HSCT.

Conflicts of interest

None.

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