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【 CASE REPORT 】

Central Nervous System-related Graft-versus-host Disease after Allogeneic Hematopoietic Stem Cell Transplantation

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Abstract:

Allogeneic hemopoietic stem cell transplantation (allo-HSCT) is the only curative therapy for refractory hematological malignancies. However, there are many treatment-related complications, including organ disorders, graft-versus-host disease (GVHD), and infectious diseases. Furthermore, there are many unclear points regarding central nervous system (CNS) complications, and the prognosis in patients with CNS complications is extremely poor. We herein report a 49-year-old woman who developed CNS-GVHD after a second transplantation for therapy-related myelodysplastic syndrome. CNS-GVHD in this case was refractory to all treatments, including steroids, and progressed. We also present a review of the literature about the symptoms, diagnosis, and treatment of CNS-GVHD.

Key words: allogeneic hematopoietic stem cell transplantation, graft-versus-host disease, central nervous system complications, central nervous system graft-versus-host disease

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Introduction

Although an effective anti-tumor effect can be achieved through conditioning regimens and donor cells in allogeneic hemopoietic stem cell transplantation (allo-HSCT), there are many treatment-related complications, including organ disorders, graft-versus-host disease (GVHD), and infectious diseases, the prevention and treatment of which are important to improve the survival rate. Of these, there are many unclear points regarding central nervous system (CNS) complications. Since the prognosis of patients with CNS complications is extremely poor, an accurate diagnosis and early therapeutic intervention when neurological symptoms occur are important. In a report by Sakellari et al. with 758 cases of allo-HSCT, 16.8% were found to have CNS complications, with the most common complication being infection (37.3%) (1). In contrast, among non-infectious causes, the most common cause was the recurrence of the original disease in the CNS (17.4%), microthrombosis (9.4%), and hemorrhaging (5.2%).

The frequency of GVHD has steadily declined due to the recent increase in the use of human leukocyte antigen (HLA) analyses and advanced immunosuppressive drugs. However, it is the main cause of relapse-free death. The skin, digestive tract, and liver are considered the main target organs of GVHD; however, all organs aside are potential targets, and the pathological conditions are varied. Although CNS-GVHD is a cerebrovascular disease or acute/chronic inflammatory demyelinating polyneuropathy, its frequency is rare, its diagnosis is often difficult, and there is no standardized treatment (1).

We herein report the results of the pathological examination of a case of progressive consciousness disorder post-allo-HSCT suspected of being CNS-GVHD based on the clinical course and a review of related published reports.

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Case Report

The patient was a 49-year-old woman with no relevant family history. She had a history of ovarian cyst and anal cancer treated with fluorouracil, mitomycin C, and 54 Gy of radiation. Pancytopenia was observed from December Year X-2. A bone marrow examination in January Year X-1 revealed two strains of dysplasia and chromosomal abnormalities [complex karyotype: 44, XX, -5, del(7)(q?), -8, add(12)(p11.2), -14, add(17)(p11.2), -18, +mar1, +mar2 (2 cells)/45, idem, -add(17), +18, -21, +mar3, +mar4 (4 cells)]; an increase in the proportion of blast cells in the bone marrow (>5%) was observed, and therapy-related myelodysplastic syndrome (MDS) [therapy-related myeloid neoplasms, WHO 2016 (Revised International Prognostic Scoring System: very high)] was diagnosed (2).

Seven courses of azacitidine (AZA) therapy resulted in complete hematological remission; an unrelated allogeneic bone marrow transplantation [HLA allele full match (8/8)] was performed in late September, Year X-1. There were a few complications, such as GVHD, and the patient was discharged on day 52 post-transplantation. At discharge, the patient was only on the immunosuppressant tacrolimus (5 mg/day) and had no symptoms of GVHD. However, pancytopenia reappeared in April Year X (7 months after transplantation), and a bone marrow examination in the same month with fluorescence in situ hybridization for the X and Y chromosomes showed the following: recipient, 15.5%; and chromosomal abnormality with complex karyotype 45, X, add(X)(p22.1), -4, der(5;17)(p10;q10), add(7)(q22), -8, add(12)(p11.2), +2mar. Therefore, the patient was diagnosed with MDS recurrence. Despite two courses of AZA therapy, the pancytopenia did not improve, so a second allogeneic hematopoietic stem cell transplantation was scheduled, and the patient was hospitalized in early August, Year X.

The physical findings on admission showed no obvious abnormalities except for palpebral conjunctival pallor. The laboratory findings on admission showed pancytopenia (white blood cell count, 1,700/μL; hemoglobin, 7.3 g/dL; platelet count, 2.1×10^4/μL), but no blast cells were observed in the peripheral blood. We observed mild renal dysfunction after the previous allo-HSCT (creatinine 1.35 mg/dL, estimated glomerular filtration rate 34 mL/min/m^2) and elevation of the biliary enzyme levels (alkaline phosphatase, 1,397 IU/L; γ-glutamyl transpeptidase, 398 IU/L). There were no other notable findings.

Unrelated allogeneic bone marrow transplantation [HLA allele full match (8/8)] was performed in late August, year X, with the following conditioning regimen: fludarabine (30 mg/m^2; day -7 to -2), busulfan (3.2 mg/kg; day -5 to day -4), and melphalan (40 mg/m^2; day -3 to day -2). For GVHD prevention, tacrolimus + short-term methotrexate [day 1 (15 mg/m^2), day 3 (10 mg/m^2), and day 6 (10 mg/m^2) after transplantation] were administered. Engraftment of neutrophils on day 20, erythrocytes on day 29, and platelets on day 31 was confirmed. The chimerism observed after bone marrow transplantation showed over 90% donor cells on days 45 and 112.

From day 24 post-transplantation, the patient complained of weakness in her limbs; her energy gradually decreased, and her consciousness gradually deteriorated. On day 34, as indicated by the Japan Coma Scale II-20, flaccid paralysis of both upper and lower limbs was observed, and an increase in the deep reflex (tendon reflex/Chaddock reflex) was observed. Magnetic resonance imaging (MRI) on the same day showed a high-frequency signal in the diffusion-weighted image of the posterior aspect of the periventricular white matter, suggesting reversible occipital leukoencephalopathy, and tacrolimus was discontinued (Fig. 1). Despite having started prednisolone (1 mg/kg/day) after tacrolimus was discontinued, acute GVHD grade II (skin, stage 3; gut, stage 1; and liver, stage 0) appeared. Electroencephalography and single-photon emission computed tomography of the brain were performed, but no specific findings were obtained. In the cerebrospinal fluid on day 34, the cell count was less than 1, total protein level was 55 mg/dL, sugar level was 83 mg/dL, lactate dehydrogenase level was 24 U/L, cytology was negative, and various viral tests (herpes simplex virus type 1, herpes simplex virus type 2, varicella-zoster virus, poliovirus, human herpes virus 6, human herpes virus 7, human herpes virus 8, cytomegalovirus, BK virus, JC virus, Epstein-Barr virus, and hepatitis B Virus) were negative.

By day 37 post-transplantation, the lesion had expanded to the corpus callosum and pons; it was thus suggested that the condition might have been caused by an inflammatory state, such as that induced by drugs and GVHD. Therefore, we started methylprednisolone pulse treatment (1 g/day for 3 days) on the same day, and immunized globulin (20 g) was administered on day 39. After methylprednisolone pulse treatment (1 g/day for 3 days), GVHD of the skin and gut gradually improved and there was no recurrence of non-CNS-GVHD. Antibiotics, antifungal agents, and proton pump inhibitors were all changed. Cyclosporin, which was started on day 66 for the treatment of CNS-GVHD, was stopped on day 99 because no clinical improvement had been noted on day 83. We observed bilateral interstitial pneumonia and respiratory syncytial virus antigen positivity; treatment with antibiotics failed, and the respiratory status worsened. Subsequently, brainstem dysfunction progressed, and light reflex, vomiting reflex, and spontaneous breathing disappeared. Respiratory failure and heart failure progressed, and a fatal cardiopulmonary arrest occurred on day 131.

A pathological examination revealed a 4-mm hematoma on the posterior surface of the neurohypophysis, severe degeneration of the occipital lobe white matter, and hemorrhaging and degeneration in the brain stem. A histological examination showed severe degeneration and unclear nerve cells. CD3-positive lymphocytes and macrophage infiltration from the subarachnoid space into the Virchow-Robin space with widespread white matter edema and spongiosis were

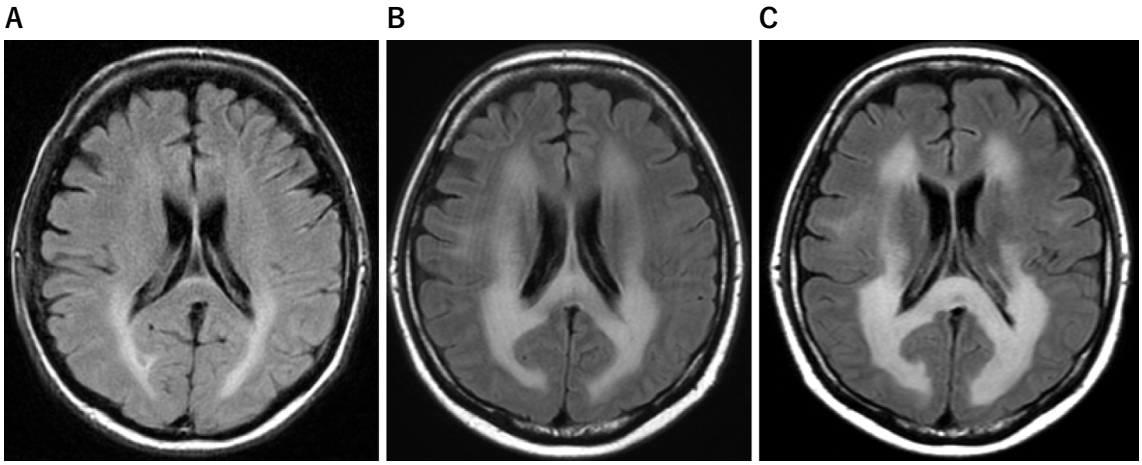

Figure 1. **Magnetic resonance imaging findings (fluid-attenuated inversion-recovery). (A) Day 34: a high-frequency signal was observed in the occipital white matter. (B) Day 63: extension of the high-frequency signal to the corpus callosum/pons was observed. (C) Day 83: the high-frequency signal in the occipital lobe had expanded further and extended to the frontal lobe.**

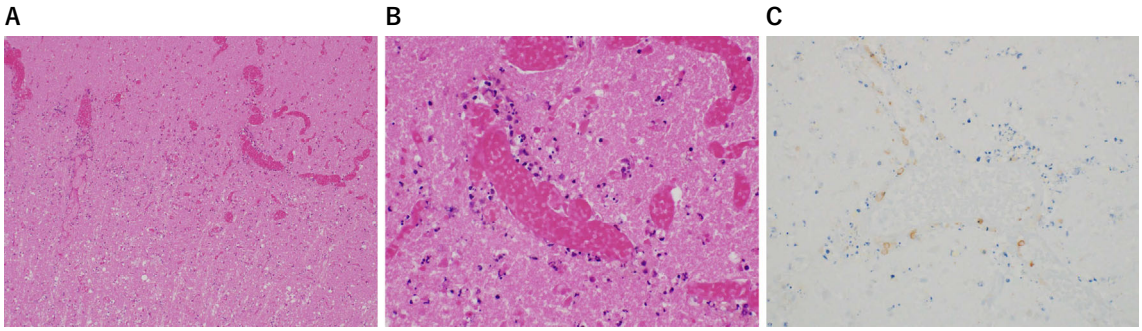

Figure 2. **Central autopsy pathological findings. (A) Hematoxylin and Eosin (H&E) staining, low power (10×): congestion and perivascular inflammatory cell infiltration in the cerebral cortex and edema in the white matter were observed. (B) H&E staining, high power (40×): cell infiltration was observed in the Virchow-Robin cavity around the cortical blood vessels. (C) Immunostaining for CD3: infiltration by CD3-positive T cells was observed.**

observed, but other immunostaining findings were unclear. The autopsy results suggested GVHD (Fig. 2).

Discussion

To diagnose CNS-GVHD, other potential causes of neurological symptoms, such as infections, autoimmune disease, vascular disease, and recurrence of primary disease, must be ruled out through physical and neurological examinations, imaging (MRI/computed tomography), electroencephalograms, electromyograms, and cerebrospinal fluid examinations. The 2009 Consensus Conference on Clinical Practice for chronic GVHD suggest that CNS-GVHD exists when the following six diagnostic criteria or criteria [1], [2], plus two or more of [3] to [6] are satisfied: [1] chronic GVHD affecting other organs, [2] central neurological symptoms not explained otherwise, [3] MRI findings corresponding to the symptoms, [4] abnormal cerebrospinal fluid findings, [5] GVHD findings through a brain biopsy or post-mortem biopsy, and [6] response to immunosuppressive therapy (3, 4). In the present case, criteria [2], [3], and [5] were satisfied, but no response to immunosuppressive therapy was observed; therefore, these diagnostic criteria were not met.

Symptoms of CNS-GVHD are diverse and non-specific, including convulsions, consciousness-related symptoms, motor and sensory symptoms, dysarthria, aphasia, weakness, and paralysis. Histologically, the infiltration of CD8-positive T cells around the cerebrovascular areas rather than that of CD4-positive T cells is often observed, and although such observations aid in diagnosing CNS-GVHD, they cannot confirm the diagnosis if present alone. A high-dose steroid trial may be performed to make a therapeutic diagnosis (4).

We searched the keywords “central nervous system” and “GVHD” in PubMed and selected English articles covering case reports published between 1990 and 2020. A total of 42 cases of CNS-GVHD have been reported so far. The median age was 36 years old (range, 7-68 years old), and the median time of the onset was 390 days (range, 7-7,300

Table. **Review of CNS-GVHD.**

Reference	Age (years)	Gender	Primary disease	Transplant	MAC/RIC	TBI	aGVHD	Severity	cGVHD	Severity	Onset (day, month, year)	Status (primary disease)	Symptoms/disorders	MRI:WMH location	CSF Findings	Tissue (inflammation, lymphocyte infiltration)	Treatment	Response	Outcome
9	32	M	CML	MRD	NR	NR	+	IV	+	NR	556D	CR	Others	NR	-	+	NA	NA	Death
10	9	M	AA	MRD	NR	NR	+	NR	+	NR	240D	CR	Consciousness disorder, convulsions	-	Protein increase, cell count increase	+	NA	NA	Death
	13	F	ALL	MRD	NR	NR	NR		+	NR	17D	CR	Others	Cerebrum	NR	+	NA	NA	Death
11	14	F	LBL	MRD	MAC	+	+	II	NR		71D	CR	Consciousness disorder, others	Cerebrum	Protein increase	NR	Steroids	PR	Death
12	43	M	CML	NR	NR	NR	+	NR	+	NR	18M	NR	Paralysis, others	-	Protein increase	+	Steroids, Cyclophosphamide	CR	Death
	32	F	AML	NR	NR	NR	+	NR	+	NR	28M	NR	Paralysis, others	-	-	NR	Steroids, Cyclophosphamide	PD	Death
	19	M	ALL	NR	NR	NR	+	NR	+	NR	31M	NR	Consciousness disorder, paralysis	Cerebrum	-	NR	Steroids	CR	Lived
	32	M	CML	NR	NR	NR	+	NR	+	NR	5Y	NR	Others	Cerebrum	-	NR	Steroids, Cyclophosphamide	SD	Lived
	53	M	CML	NR	NR	NR	+	NR	+	NR	30M	NR	Others	Cerebrum	Cell count increase	NR	NA	PD	NR
13	22	F	ALL	(M)UD	MAC	+	+	II	-		NR	CR	Paralysis	Cerebrum	NR	NR	Steroids	CR	NR
14	24	F	LBL	haplo	NR	NR	+	II	+	NR	380D	CR	Others	Cerebellum/pons	Oligoclonal band, lymphocytocis	NR	Steroids, plasma exchange	Transient	NR
15	18	F	AML	UD	NR	NR	+	NR	NR		2M	NR	Convulsions	-	Protein, lymphocytosis	+	Steroids	PR	NR
16	48	F	AML	MRD	MAC	+	+	II	+	NR	10M	CR	Others	Cerebrum	-	NR	NR	CR	Lived
17	55	F	NHL	MRD	NR	NR	+	NR	-		23M	CR	Others	Cerebrum	NR	NR	Tacrolimus	PR	Lived
18	47	M	FL	MUD	RIC	-	+	NR	-		425D	CR	Convulsions, others	Cerebrum	Protein increase, lymphocytosis	NR	Steroids	CR	Lived
19	54	M	AML	MRD	NR	NR	NR	NR	NR	NR	390D	NR	Others	Cerebrum	Protein increase	-	Steroids, IVIG	PR	Death
	59	M	AML	MRD	NR	NR	NR	NR	NR	NR	240D	NR	Others	Pons	Protein increase, oligoclonal band	NR	IVIG	PR	Lived
	29	F	AML	MRD	NR	NR	NR	NR	NR	NR	63D	NR	Others	Cerebrum	Protein increase, oligoclonal band	-	Steroids, IVIG	PR	Death
7	44	F	TCL	MRD	MAC	+	+	I	+	Mild	18M	CR	Convulsions, paralysis	Cerebrum	-	+	Steroids	CR	Lived
	58	F	ALL	UD	RIC	+	+	II	+	Mild	178D	CR	Convulsions, others	Cerebrum	Protein increase	+	Steroids	Transient	Death
20	41	M	FL	MRD	MAC	-	NR		+	NR	18M	CR	Paralysis	Cerebrum	-	+	Steroids, Cyclosporine	PR	Lived
21	32	F	MDS	MRD	MAC	-	-		+	NR	7M	CR	Others	Cerebrum	-	NR	Steroids, Cyclosporine	PR	Lived
22	56	M	NHL	NR(PB)	RIC	NR	NR		+	Mild	3Y	CR	Others	Cerebrum	NR	+	Steroids, MMF	PD	Death
23	40	F	FL	CB	RIC	+	-		NR		7D	CR	Consciousness disorder, convulsions	-	Protein increase, cell count increase	NR	Steroids, Etoposide	PD	Death
24	35	M	CML	MUD	NR	NR	+	III	+	Moderate	4Y	CR	Convulsions	-	NR	-	Steroids, Cyclosporine, Methotrexate	CR	Lived
	28	F	AML	MUD	NR	NR	+	III	+	Moderate	2Y	CR	Motor impairment, paralysis, others	Cerebrum	Protein increase, oligoclonal band	+	Steroids, Cyclophosphamide	CR	Lived
	20	M	SCID	haplo	NR	NR	-		+	Atypical	20Y	CR	Motor impairment, paralysis, others	-	Protein increase, cell count increase	+	Steroids, Cyclophosphamide	PR	Death
	33	M	CLL	MUD	NR	NR	+	III	+	Moderate	2Y	CR	Motor impairment, convulsions, paralysis, others	-	Protein increase, cell count increase, IgG increase	+	Steroids, Cyclophosphamide	PR	Death
25	57	M	CMML	MUD	MAC	-	-		-		4W	CR	Paralysis, others	Spinal cord	Protein increase	NR	Steroids, Cyclophosphamide	CR, recurrence	Lived
	65	M	AML	MRD	RIC	+	-		-		3Y	CR	Paralysis, others	Spinal cord	Protein increase, oligoclonal band	NR	Steroids	CR, recurrence	Lived
26	63	M	CLL	MUD	RIC	+	+	II	-		92D	CR	Motor impairment, others	Cerebrum	Protein increase	NR	Steroids	CR	Lived
27	7	M	AA	MRD	NR	NR	-		+	NR	15M	CR	Convulsions, others	Cerebrum	-	NR	Steroids, IVIG	CR	NR
5	33	M	Fanconi anemia	MRD	RIC	+	+	I	+	Severe	308D	CR	Motor impairment, others	-	Protein increase, oligoclonal band, lymphocytosis	+	Steroids, MMF	PR	Lived
	62	M	MPN	UD	MAC	-	+	III	-		152D	CR	Consciousness disorder	-	Protein increase, lymphocytosis	+	Steroids	No R	Death
	68	F	MPN	MUD	MAC	-	+	III	-		9D	CR	Consciousness disorder	Cerebrum	Lymphocytosis	NR	Steroids	No R	Death
	29	F	Fanconi anemia	CB	RIC	NR	-		+	Severe	378D	NR	Others	-	Protein increase	NR	Steroids, plasma exchange, IVIG	PR	Death
	50	M	MPN	MRD	MAC	NR	-		+	Moderate	2590D	NR	Paralysis, others	-	-	NR	Cyclosporine	CR	Lived
	16	F	AML	UD	MAC	NR	+	I	-		255D	NR	Others	Multiple areas, cerebellum	-	NR	Steroids	No R	Death
	36	M	CML	MRD	MAC	NR	+	I	+	Severe	119D	NR	Paralysis, others	-	Protein increase, IgG increase	NR	Steroids	PR	Death
6	60	M	AML	2nd MUD	RIC	+	-		-		7D	CR	Consciousness disorder, others	Cerebrum	Protein increase	NR	Steroids, MMF, Tacrolimus, CSF injection (steroids)	CR, recurrence	Death
8	35	F	MDS	MUD	RIC	-	-		+	Mild	24M	CR	Convulsions, others	Cerebrum	-	+	Steroids, Tacrolimus, plasma exchange	CR	Lived
4	68	M	MDS	UD	RIC	+	-		-		742D	CR	Others	Cerebrum	Protein increase	+	Steroids	PR	Death
Present case	49	F	MDS	2nd MUD	RIC	-	+	II	-		24D	CR	Consciousness disorder, others	Cerebrum	-	+	Steroids, Cyclosporine, IVIG	PD	Death

M: male, F: female, D: day, M: month, Y: year, AML: acute myeloid leukemia, ALL: acute lymphoblastic leukemia, CML: chronic myeloid leukamia, CLL: chronic lymphocytic leukemia, MDS: myelodysplastc syndrome, MPN: myeloproliferative neoplasms, CMML: chronic myelomonocytic leukemia, NHL: non-Hodgkin lymphoma, LBL: lymphoblastc lymphoma, FL: follicular lymphoma, AA: aplastic anemia, TCL: T cell lymphoma, SCID: severe combined immunodeficiency, MRD: matched related donor, MUD: matched unrelated donor, UD: mismatch unrelated donor, Haplo: haploidentical donor, CB: cord blood, WMH: white matter hyperintensity, MAC: myeloablative conditioning, RIC: reduced-intensity conditioning, TBI: total body irradiation, aGVHD: acute graft-versus-host disease, cGVHD: chronic graft-versus-host disease, MRI: magnetic resonance imaging, IVIG: intravenous immunoglobulin, MMF: mycophenolate mofetil, CSF: cerebrospinal fluid, CR: complete response, PR: partial response, PD: progressive disease, No R: no response, NR: not reported, NA: not available, Others: involuntary movements, weakness, sensory disorders, visual impairment, muscle weakness, personality changes, extrapyramidal symptoms, cerebellar symptoms, polyneuritis, memory disorders, depression, vertigo, cognitive disorders, urinary retention, visual impairment, dysarthria, hearing impairment, epileptic seizures, tinnitus, headache, cerebellar symptoms, aphasia

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days) after transplantation. Acute and chronic GVHD other than CNS-GVHD were observed in 87.5% (35/40) of cases. Symptoms varied, but convulsions (23.2%) and consciousness-related symptoms (18.6%) were common. Abnormal findings on MRI included gross lesions and multiple white matter lesions in almost all cases [92.9% (39/42)]; in 57.1% of the cases, lesions were found in the cerebral white matter. A cerebrospinal fluid examination showed increased protein levels and cell counts in 57.9% (22/38) and 26.3% (10/38) of cases, respectively. A histological examination might potentially have yielded the most important findings for a diagnosis, but it was performed in only 46.5% (20/44) of the cases. A biopsy revealed perivascular lymphocyte infiltration (inflammation) in 76.2% (16/21) of cases. The treatment used included steroids (1.5-2.0 mg/kg) (92.3%), and the response rate (partial remission+remission) was relatively high (77.5%, 31/40), with a remission rate of 37.5% (15/40). Only one case entered remission without the use of steroid drugs, and all seven steroid-refractory cases were fatal. The mortality rate was 55.3% (21/38) due to subsequent complications, such as relapse and infection, and the prognosis was poor (Table) (4-27).

In the present case, neurological and serological tests were performed, but the actual cause was unclear. Although all of the drugs were changed, there was no improvement, and it was deemed to be a case of CNS-GVHD based on an exclusion diagnosis and post-mortem pathological autopsy results. Histological findings are also important in the diagnosis, and a brain biopsy should also be considered during the course of the disease. As with other types of GVHD, the use of steroids is vital in the treatment of CNS-GVHD, and responsiveness to steroids is integral in its diagnosis and prognostic assessment. In cases with steroid resistance, aside from tacrolimus and cyclosporin, which are usually used for GVHD prevention, anti-thymocyte globulin and cyclophosphamide as well as new GVHD treatments, such as mesenchymal stem cells and Janus kinase (JAK) inhibitors, are also options. Although no drugs have yet been reported to be effective when administered intrathecally, the existence of the blood-brain barrier in the CNS means it is necessary to consider direct administration via the CSF and to select drugs with consideration of their CNS permeability in cases with abnormal CSF findings. Understanding the laboratory findings and clinical features and characteristics of CNS-GVHD may lead to earlier therapeutic intervention and the prevention of exacerbation; further studies are thus needed in the future.

The authors state that they have no Conflict of Interest (COI).

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