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ORIGINAL ARTICLE

Analysis of five cases of human herpesvirus-6 myelitis among 121 cord blood transplantations

Toshimitsu Ueki[1] · Kenichi Hoshi[2] · Yuki Hiroshima[1] · Masahiko Sumi[1] · Naoaki Ichikawa[1] · Masao Ogata[3] · Takako Satou[3] · Takahiro Fukuda[4] · Hikaru Kobayashi[1]

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Abstract Reports of myelitis associated with human herpesvirus-6 (HHV-6) following allogeneic transplantation are rare. Of 121 cases of cord blood transplantation (CBT) performed at Nagano Red Cross Hospital, five cases (4.1%) of HHV-6 myelitis developed at around the time of engraftment. The major symptom identified in all five patients was superficial pain or pruritus linked to segmental levels of the spinal cord. Other identified symptoms were fever or low-grade fever in all five patients, autonomic nerve disorder in four patients, bladder and rectal disturbance in two patients, and extrapyramidal disorder in two patients. These symptoms were experienced primarily 16–39 days after CBT. HHV-6 PCR tests were all positive for cerebrospinal fluid and for plasma. Of the four cases tested by magnetic resonance imaging (MRI), three showed spinal cord abnormality. Antiviral therapy using foscarnet or ganciclovir was effective in every case. Although one case treated from 12 days after onset experienced long-term pain resembling postherpetic neuralgia, symptoms in the four cases were completely relieved after antiviral therapy. In summary, the major symptoms of HHV-6 myelitis were superficial pain linked to segmental levels of the spinal cord. Prognosis may be improved by early initiation of antiviral therapy.

✉ Toshimitsu Ueki
toshimitsu-u@h9.dion.ne.jp

[1] Department of Hematology, Nagano Red Cross Hospital, Nagano, Japan

[2] Department of Neurology, Nagano Red Cross Hospital, Nagano, Japan

[3] Department of Hematology, Faculty of Medicine, Oita University, Oita, Japan

[4] Department of Hematopoietic Stem Cell Transplantation, National Cancer Center Hospital, Tokyo, Japan

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Introduction

The use of cord blood as a donor source for hematopoietic stem cell transplantation has become more common in the recent years. Transplantation using cord blood has no risk for the donor and can be performed in cases that require urgent transplantation. However, the immunological immaturity of cord blood has led to an increase in viral infections after transplantation [1–4].

Human herpesvirus-6 (HHV-6), which belongs to the *Betaherpesvirinae* subfamily, was first isolated and identified in 1986 [5]. Since then, various complications caused by this virus have been reported, especially following allogeneic transplantation [6, 7]. These complications include encephalitis, bone-marrow suppression, engraftment failure, delay of platelet engraftment, interstitial pneumonia, hepatitis, gastrointestinal lesions, and fever [8–10]. Encephalitis is particularly lethal and often produces severe sequelae such as memory loss and seizures. HHV-6 encephalitis following allogeneic stem cell transplantation has been reported to occur in 0.96–8.0% of allogeneic stem cell transplant recipients [9–14]. The risk appears to be high after cord blood transplantation [14–19].

Although encephalitis is frequently reported as a central nervous system (CNS) complication of HHV-6, few detailed reports of myelitis, especially cases showing dysautonomia, have been published [20]. Of the 121 CBTs performed at the Nagano Red Cross Hospital Transplantation Center between 2003 and 2015, five cases of HHV-6 myelitis were observed around the time of engraftment. We report their details here.

Patients and methods

Between January 1998 and February 2015, 320 allogeneic transplantations were performed at the Nagano Red Cross Hospital Transplantation Center. We retrospectively investigated all cases using the medical chart database. Donor sources included 85 cases of bone marrow or peripheral blood from relatives, 114 cases of bone marrow from unrelated donors, and 121 cases of cord blood. The details are shown in Table 1. Of the 121 CBTs, 28 were considered early stage and 93 non-early. Early stage was defined as first hematopoietic stem cell transplantation for leukemia in remission, chronic myeloid leukemia (CML), myelodysplastic syndrome (MDS) classified as refractory anemia or refractory anemia with ringed sideroblasts, lymphoma in remission, and aplastic anemia at any stage. All other cases were considered non-early. There were 45 cases involving multiple hematopoietic stem cell transplantations; we defined them as non-early cases irrespective of the disease status. The conditioning modalities for CBT included 22 myeloablative and 99 reduced intensity conditioning (RIC). For prophylaxis of graft-versus-host disease, tacrolimus (FK) alone was used most often ($n = 74$). Acyclovir was administered from day 7 before CBT in every case for prophylaxis of herpes simplex virus infection. In recent cases, copy numbers of HHV-6 DNA in plasma were regularly monitored by polymerase chain reaction (PCR). Among 74 cases monitored, 47 received planned foscarnet (FCN) prophylaxis at a dose of 90 mg/kg for HHV-6 from around day 7 to engraftment and thereafter; however, only 22 cases completed the therapy, mainly due to nephrotoxicity (completion rate: 47%). Pre-engraftment immune reaction (PIR) was defined as noninfectious fevers that developed more than 5 days before engraftment [21].

HHV-6 myelitis was diagnosed if superficial pain or pruritus at the segmental levels of the spinal cord was observed, with a positive PCR result for HHV-6 in cerebrospinal fluid (CSF), and if the symptoms could not be accounted for by other causes [14]. Other viruses which could cause myelitis (e.g., herpes simplex virus and varicella-zoster virus) were generally evaluated by PCR using CSF samples (Table 3). Cases of HHV-6 myelitis were retrospectively evaluated for detailed symptoms, examination findings, and treatment efficacy.

Table 1 Patient characteristics

Characteristics	All patients	CBT	Non-CBT	*p*
No. of transplantations	320	121	199	
Median patient age at transplantation, *y* (range)	48 (16–68)	51 (17–68)	47 (16–68)	$p = 0.0211$
Patient sex, *n* (%)				$p = 0.4121$
Male	192 (60)	69 (57)	123 (62)	
Female	128 (40)	52 (43)	76 (38)	
Disease classification				$p = 0.6234$
AML	134 (42)	58 (48)	76 (38)	
ALL	50 (16)	15 (12)	35 (18)	
MDS	42 (13)	13 (11)	29 (15)	
CML	12 (4)	4 (3)	8 (4)	
NHL	50 (16)	20 (16)	30 (15)	
AA	11 (3)	3 (2)	8 (4)	
Others	21 (7)	8 (7)	13 (6)	
Disease status				$p < 0.001$
Early	136 (43)	28 (23)	108 (54)	
Non-Early	184 (57)	93 (77)	91 (46)	
HLA matching				$p < 0.001$
0 mismatched loci	193 (60)	16 (13)	177 (89)	
1 mismatched loci	66 (21)	48 (40)	18 (9)	
2 mismatched loci	59 (18)	57 (47)	2 (1)	
3 mismatched loci	2 (1)	0 (0)	2 (1)	
Preparation regimen				$p < 0.001$
MAC	136 (43)	22 (18)	114 (57)	
RIC	184 (58)	99 (82)	85 (43)	
GVHD prophylaxis				$p < 0.001$
CI alone	95 (30)	74 (61)	21 (11)	
CI + MTX	180 (56)	11 (9)	169 (85)	
CI + MMF	45 (14)	36 (30)	9 (5)	

Early stage is defined as: First hematopoietic stem cell transplantation of leukemias in remission; CML in chronic phase; MDS classified as refractory anemia or refractory anemia with ringed sideroblasts; lymphoma in remission; any stage of aplastic anemia. All others are considered nonearly stage

MAC myeloablative conditioning, *RIC* reduced intensity conditioning, *CI* calcineurin inhibitor including cyclosporine and tacrolimus, *MTX* methotrexate

Results

Five cases were diagnosed as HHV-6 myelitis ($n = 121$), with onset between 16 and 39 days (median, 23 days) after CBT, at an incidence rate of 4.2%. None of those who received bone marrow or peripheral blood ($n = 199$) developed myelitis. Details of the myelitis cases are shown in Tables 2 and 3. PIR developed in every case, and steroid therapy was initiated for each patient. Among 74 cases in which plasma PCR was performed, the proportion of reactivation and high-level reactivation (plasma HHV-6

Table 2 Backgrounds of the myelitis cases

Case	Age	Sex	Disease	Disease status	Times of HSCT	HLA disparities GVH/HVG	Infused cells × 10^7/kg	Conditioning regimen	GVHD prophylaxis	Preceding PIR occuring at	Preceding use of steroids (PSL) (mg/kg)	Engraftment
1	34	M	CML	CP2	2	4/4	1.62	Flu/Cy/TBI	FK	d7	2	d18
2	57	M	MDS	RAEBII	1	6/6	1.57	Flu/Mel/TBI	FK	d9	0.2	d31
3	57	M	AML	NCR	1	5/5	3.03	Flu/Mel/TBI	FK	d9	2	d35
4	56	M	AML	PIF	1	4/4	3.50	Flu/Mel/TBI	FK	d5	10	d35
5	62	M	PTCL	RL2	1	5/5	2.10	Flu/Mel/TBI	FK MMF	d7	1	d21

CML chronic myeloid leukemia, *MDS* Myelodysplastic syndrome, *AML* acute myeloid leukemia, *PTCL* peripheral T cell lymphoma, *CP* Chronic phase, *RAEB* refractory anemia with excessive of blasts, *NCR* no complete remission, *PIF* primary induction failure, *RL* relapse, *Flu* fludarabine, *Cy* cyclophosphamide, *Mel* melpharan, *TBI* total body irradiation, *FK* tacrolimus, *MMF* mycophenolate mofetil, *PIR* pre-engraftment immune reaction, *PSL* prednisolone, *d* days after transplantation

DNA ≥ 10^4 copies/mL) was 81.1% (60/74) and 28.4% (21/74), respectively. Two of the 21 cases of high-level reactivation developed HHV-6 myelitis.

The primary symptoms in all five cases were severe pain or pruritus coinciding with specific dermatomes. In all cases, the onset of severe pain or pruritus was restricted to a relatively narrow range of dermatomes. After several days, the symptoms spread to a wider area. In one case, 50 mg/kg FCN was administered as prophylaxis against HHV-6 reactivation. In the remaining four cases, acyclovir was administered at onset of myelitis for prophylaxis against herpes simplex virus. None of the cases had vesicular cutaneous lesions indicative of herpes simplex virus or varicella-zoster virus infection. Although narcotics such as morphine, oxycodone, and fentanyl did not provide sufficient pain control in all five cases, ketamine treatment combined with morphine appeared to be effective for lancinating pain in cases 1 and 3. Pain control with narcotics was continued until severe pain was relieved. The duration of narcotics treatment was 9–51 days from the onset of myelitis in four cases (cases 2, 3, 4, and 5). Case 1 was administered fentanyl for 4 years until lancinating pain was finally relieved.

Other identified symptoms included fever or low-grade fevers (which were refractory to antibiotics or antifungals, were not explained by any other causes, and were noted after PIR symptoms resolved due to steroids) in all five cases, autonomic nerve disorder in four, bladder and rectal disturbance in two, and myoclonus in two. Three of the five cases presented with autonomic nervous symptoms such as hyperhidrosis, sinus tachycardia attacks, and high blood pressure (− 7 to 4 days after the onset of myelitis). Significant intermittent flushing and hyperhidrosis were observed in cases 1 and 5, requiring 2–3 L supplementary fluid per day for 3 weeks (case 1) or 1 week (case 5). Hyponatremia due to hyperhidrosis was also observed in these two cases. Intermittent sinus tachycardia attacks (> 120 up to 160/min) that lasted for a few minutes repeatedly for 2–3 weeks were also noted in cases 1, 3, and 4. High blood pressure (> 160 up to 200 mmHg) was also noted in cases 1, 3, and 4 for 2 or 3 weeks.

In two of the five cases (cases 1 and 3), bladder–rectal disturbance was observed 2 days after onset, requiring a catheter for the spastic bladder in both cases. Cases 1 and 5 also developed myoclonus of the limbs. These symptoms appeared 2 days after the onset of myelitis and lasted about a week. Cases 2 and 5 also had short-term memory loss. Although magnetic resonance imaging (MRI) revealed no atrophic changes in the bilateral hippocampus, a diagnosis of limbic encephalitis was made in accordance with the diagnostic criteria (which consisted of typical symptoms of short-term memory loss and positive HHV-6 PCR in CSF). [16] These symptoms were observed 2 days after the onset of myelitis.

Table 3 Symptoms, examination, therapy, and outcomes of myelitis

Case	Symptoms										Examination								Therapy		Outcome	
	Symptom at onset	Initinal pain levels of spinal cord	Onset	Sensory		Autonomic disorders			Bladder–rectal disturbance	Myoclonus	Encephalopathy	MRI		CSF		HHV6 PCR (copies/ml)		Other viruses		Antiviral drugs.start days after myelitis onset	Duration of antiviral drugs. days	Result (days after transplantion)	Cause of death
				Pain	Pruritus	Hyperhydrosis	Sinus tachycardia	Paralytic ilues				Spinal cord	Brain	Cell (/μL)	Protein (mg/dL)	CSF	Plasma	CSF	Blood				
1	Pruritus	C2-T4	d16	+ 0	+ 0	+ 1	+ 1		+ 2	+ 2		n.p	n.p	5	24	54,000	n.e.	HSV PCR(−) VZV PCR(−) CMV PCR(−) JCV PCR(−)	C7-HRP(-)	GCV day 12	29	Alive 2525+	
2	Chest Pain	T4-5	d20	+ 0							+ 3	Figure 2	n.p	3	43	670	47	n.e	C7-HRP(-)	GCV day 9	27	Dead 264	Relapse
3	Diminished sensation	T2-10	d25	+ 0			+ 4	+ 2	+ 2			Figure 3	n.e	5	53	280,000	4200	HSV PCR(−) VZV PCR (−)	C7-HRP(−)	FCN day 0	7	Dead 77	Relapse
4	Abdominal Pain	T6-12	d39	+ 0			− 7					Figure 4	n.e	0	45	11,646	28,385	HSV PCR(−) VZV PCR(−) CMV PCR(−)	C7-HRP(−)	GCV day 0	14	Dead 545	Relapse
5	Pruritus	T1-12	d23		+ 0	+ 0				+ 2	+ 2	n.e.	n.p	3	59	12,126	39,243	HSV PCR(−) VZV PCR(−)	C7-HRP(−)	GCV day − 3	9	Alive993+	

Examination, therapy, and outcomes of myelitis are shown in Table 3. Clinical courses of each case including main symptoms, HHV-6 DNA copy numbers, and myelitis therapies are shown in Fig. 1. Spinal cord MRI was performed in four cases. In cases 2, 3 and 4, high signal intensity was detected on short TI inversion recovery (STIR)

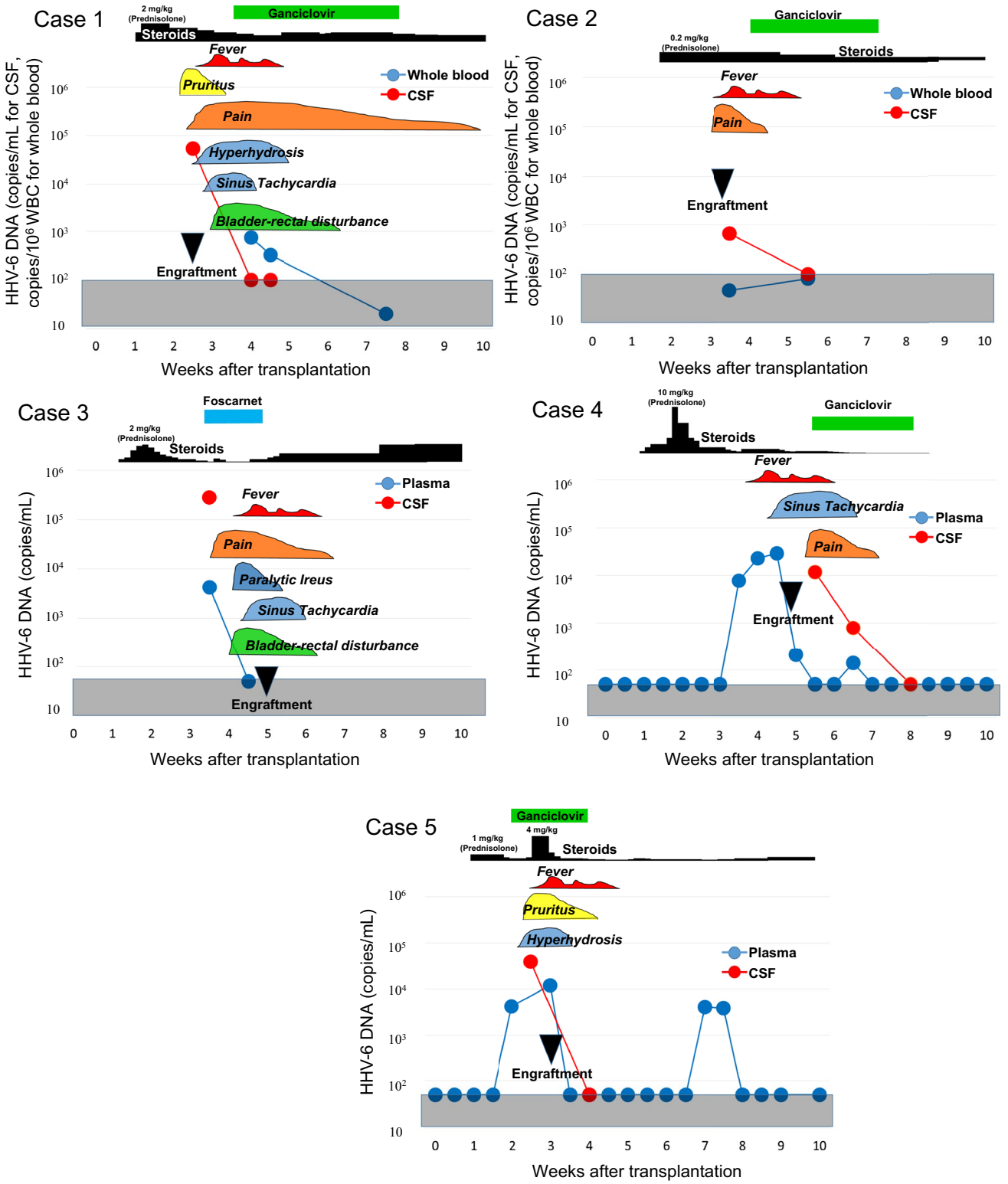

Fig. 1 Clinical courses of HHV-6 myelitis cases

images around the central canal at spinal cord positions coinciding with the dermatomes where pain was experienced (Figs. 2, 3, and 4). No abnormal findings were obtained for case 1. HHV-6 DNA PCR analysis of CSF was positive (670–280,000 copies/mL) for all cases. The analysis was performed at onset using whole blood (cases 1, 2) or plasma (cases 3, 4, 5) samples. General CSF examination was performed in all five cases; only a slightly elevated cell count and/or slightly increased protein levels were obtained. None of the cultures of CSF in these five cases were positive for bacterial or fungal infection. Other viruses that could cause myelitis, such as herpes simplex virus and varicella-zoster virus, were generally evaluated by PCR using CSF samples, revealing negative results. Three of the five cases were started on FCN prophylaxis, although two discontinued prior to myelitis onset due to nephrotoxicity. The only case that could continue FCN, but eventually developed HHV-6 myelitis, was treated at a dose of 50 mg/kg, which is thought to be insufficient to prevent HHV-6 CNS complications [22].

Pain control was extremely difficult; diazepam, morphine, and xylocaine were generally ineffective, although ketamine was effective in two cases. In two (cases 1 and 3) of the five cases, bilateral leg pain was observed, suggesting the possibility of calcineurin inhibitor pain syndrome (CIPS). Ganciclovir (GCV) or FCN was started in all cases around the onset (day − 3 to + 12), and myelitis symptoms improved. Four cases were treated with 10 mg/kg GCV, and one case with 180 mg/kg FCV. In case 5, GCV was started 3 days before onset because cytomegalovirus antigen was detected by weekly monitoring. These antivirals were continued until 7–29 days after onset. Outcomes did not include any deaths directly attributable to myelitis. Disease-free survival was achieved in two cases; three died due to relapse of the primary disease.

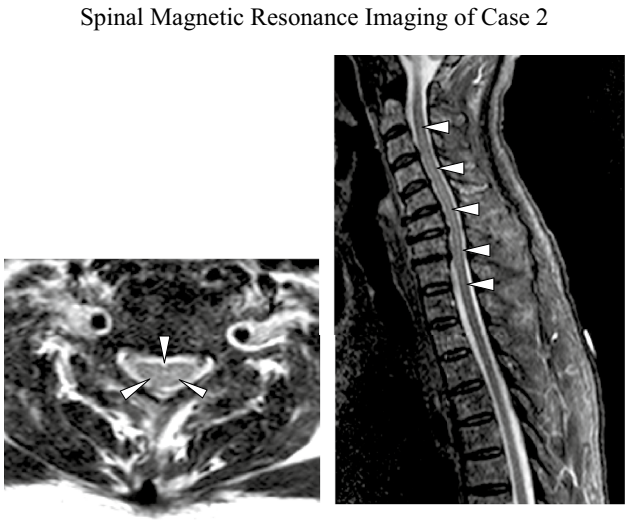

Fig. 2 Spinal magnetic resonance imaging of case 2. High signal intensity was detected on short TI inversion recovery (STIR) images around the central canal at spinal cord positions coinciding with the dermatomes where pain was experienced

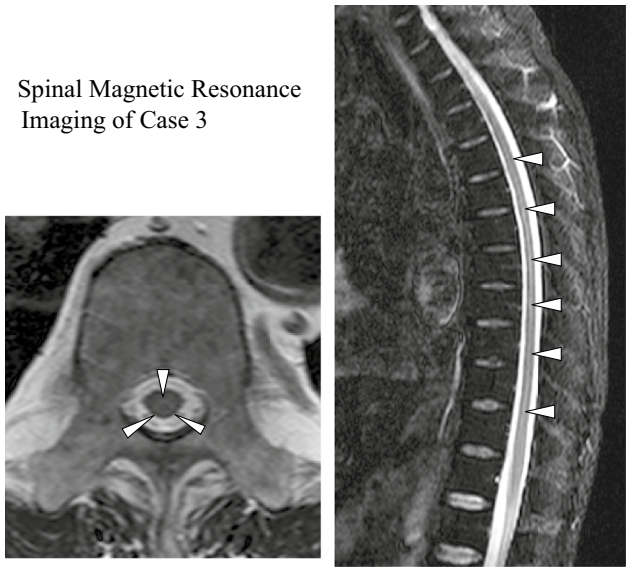

Fig. 3 Spinal magnetic resonance imaging of case 3. High signal intensity was detected on short TI inversion recovery (STIR) images around the central canal at spinal cord positions coinciding with the dermatomes where pain was experienced

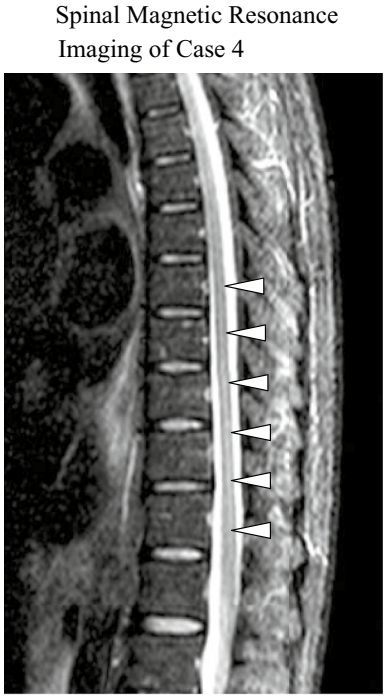

Fig. 4 Spinal magnetic resonance imaging of case 4. High signal intensity was detected on short TI inversion recovery (STIR) images around the central canal at spinal cord positions coinciding with the dermatomes where pain was experienced

Discussion

HHV-6-associated myelitis following CBT was first reported by Mori et al. as a rare complication, with the primary presenting symptoms being abnormal sensations and bladder–rectal disturbances [23]. In 2010, Mori et al. reported that HHV-6 myelitis, presenting as bilateral leg pain similar to CIPS, has a higher risk in CBT [14]. However, detailed symptoms of HHV-6 myelitis and its biological mechanisms have not been reported. In the present study, HHV-6 was assessed by DNA PCR analysis of CSF in all five cases.

HHV-6 produces exanthem subitum in childhood and causes latent infections in peripheral blood mononuclear cells, salivary glands, and glia cells in the CNS [24–27]. Ito et al. reported that among patients with HIV or hematological diseases, brain biopsies in cases of HHV-6 encephalitis showed numerous HHV-6-positive glial cells, apparently through reactivation of the virus by immunodeficiency [28]. Shintaku et al. reported that in the autopsy of a patient with HHV-6 encephalomyelitis after hematopoietic stem cell transplantation, dropout and necrosis of nerve cells and demyelinating lesions were detected at the limbic cortex, cerebral cortex, and anterior horn of the spinal cord [29]. These findings suggest that following transplantation, the HHV-6 virus attacks nerve cells and the myelin sheath after reactivation within glial cells.

All five patients experienced onset of severe pain or pruritus in a narrow range of dermatomes, suggesting dysfunction of pain-sensing nerves. Given that symptoms were bilateral in all cases, bilateral failure in the pain-sensing nerves is likely, with dysfunction occurring first from the vicinity of the central canal of the spinal cord to the site of the posterior horn. The number of affected dermatomes rapidly increased over several days. Afterwards, the symptoms progressed to dysautonomia and bladder–rectal disturbances. During this progression, some patients showed extrapyramidal symptoms such as tremors and rigidity.

The autonomic nucleus, which is the center of sympathetic nerves, is located at the lateral horn of the spinal cord. The reticulospinal tract, which controls the autonomic nucleus from higher order neurons, runs along the white matter slightly exterior to the lateral horn. The myelitis symptoms suggest that the primary site of inflammation is initially located in the region of central canal to the posterior horn, and also involves the lateral horn. Three of the five cases in this study were positive for myelitis by spinal cord MRI. STIR imaging revealed a tubular high intensity signal surrounding the central canal, coinciding with the dermatome of pain. This finding could explain the symptoms of bilateral pain and pruritus developing in a narrow range of dermatomes. In one case (case 1), no MRI findings were obtained despite severe symptoms. Mori et al. reported that MRI of the spine showed multiple abnormal T2-high lesions only in one of four HHV-6 myelitis cases [14]. Thus, the sensitivity of MRI for HHV-6 myelitis might not be as high as for HHV-6 encephalitis.

CNS glial cells maintain the appropriate concentration of glutamic acid, which is one of the excitatory neurotransmitters. Reactivation of dormant HHV-6 in CNS glia cells may alter the glutamic acid incorporation and glutamate transporter expression in neurons. Fotheringham et al. reported that infection of glioma cells with HHV-6 initially increases glutamic acid incorporation, but subsequently decreases incorporation, resulting in deranged glutamic acid metabolism [30]. Unmyelinated C-fibers transmit pruritus and dull pain, whereas myelinated Aβ-fibers transmit sharp, severe pains; glutamic acid acts as a transmitter for both types of nerve cells [31]. Thus, a hypothesis can be postulated that neurons near damaged glia cells are influenced by excessive amounts of glutamic acid, thereby inducing severe pruritus and sharp pain in the early stage. In three of the five cases, pain control was extremely difficult. Diazepam, morphine, and xylocaine, were generally ineffective, although ketamine, an antagonist of NMDA (glutamate) receptors in neurons, was effective in two cases. Thus, our hypothesis is supported by the observation that acute pain was lessened by ketamine treatment [32].

HHV-6 encephalitis develops 2–6 weeks after transplantation, around the time of engraftment [33, 34]. The timing of onset for myelitis was very similar to that of HHV-6 encephalitis. PIR was detected in all five cases, and steroid therapy was initiated. In all cases, reduced intensity conditioning was carried out. In each of the five cases, transplantation was performed during a progressive stage or as secondary transplantations. The following risk factors have been reported for HHV-6 infection of the CNS: transplantation at a later stage, PIR [14], CBT [14, 19], mismatch transplantation, high levels of interleukin-6, and steroid use [13]. In the present study, the myelitis cases had most of these risk factors. As we reported previously, PIR may exert anti-tumor effects [15]. Therefore, proper management of post-PIR HHV-6 related complications might improve CBT results.

Ogata et al. reported that high levels of plasma HHV-6 DNA are associated with higher risk of HHV-6 encephalitis [16]. Consistently, we found that among the 74 plasma PCR-monitored cases in our study, none of the 53 cases without high-level HHV-6 reactivation developed HHV-6 myelitis, whereas 2 of the 21 cases (9.5%) with high-level HHV-6 reactivation developed HHV-6 myelitis.

CIPS following hematopoietic stem cell transplantation was first reported by Kida et al. as a rare complication accompanied by pain in both legs and accumulation in the distal end of the long bone as assessed by bone scintigraphy [35]. There have since been five case reports of CIPS-like symptoms before or following hematopoietic stem cell

Table 4 Previous reports of CIPS-like symptoms before or following hematopoietic stem cell transplantation

Study	Diagnosis	Age(y)	Sex	HSCT type	Times of HSCT	Preceding PIR or GVHD	Preceding use of steroids	Onset (after transplantation)	Severe pain	Pruritus	Clinical signs of dysautonomia	Therapy	Response	Result
Kida et al. [35]	NA	51	M	NA	NA	Yes	Yes	10 months	Bl. lower limbs	NA	n.a	NA	NA	NA
Kida et al. [35]	AML	18	F	UCBT	2	NA	NA	day 18	Bl. lower limbs	Yes	n.a	Painkiller	No	Died d9 of respiratory failure
	ALL	32	M	UCBT	1	Yes	Yes	day 12	Bl. lower limbs	Yes	Hypertention	Discontinue FK, Calicium channel blocker. and Painkiller	Yes	Improved
Takashima. et al. [37] Noda et al. [38]	ALL	42	F	UBMT	2	Yes	Yes	day 21	Rt. lower abdominal and limbs	Yes	No	Discontinue FK, Calicium channel blocker, and Painkiller	Yes for lidocaine	Improved
Lavoratore et al. [39]	AML	6	NA	NA	2	–	–	day − 3	Bl. lower limbs	NA	n.a	Discontinue CyA	Yes	Improved

HSCT hematopoietic stem cell transplantation, *Bl* bilateral, *Rt* right, *FK* tacrolimus, *CyA* cicrosporin, *n.a* not assesed, *AML* acute myeloid leukemia, *ALL* acute lymphoblastic leukemia, *UCBT* unrelated cord blood transplantation, *UBMT* unrelated bone marrow transplantation

transplantation (Table 4) [35–39]. Only one report showed positive bone scintigraphy, whereas in the other reports, leg pain characteristic of CIPS was diagnosed as CIPS by eliminating other conditions that could have caused the pain. HHV-6 DNA PCR tests were not conducted in any of the cases.

Mori et al. suggested the possibility of HHV-6 myelitis in several of these reports. If one compares previous cases reported as CIPS to those of the present study, many commonalities emerge: in several reports, there were cases in which the time of onset was around the time of engraftment; onset occurred after CBT in some cases; onset occurred after multiple HSCT; symptoms included characteristic bilateral, intermittent fulminant pain that was resistant to various analgesic drugs and adjuvants; and one case was accompanied by autonomic symptoms such as high blood pressure. Thus, it is likely that some of the previously reported CIPS cases may have involved HHV-6 myelitis. For cases involving CIPS-like pain following hematopoietic stem cell transplantation, and particularly after cord blood transplantation, it is possible that termination of calcineurin inhibitor followed by use of other immunosuppressants such as steroids for GVHD prevention may worsen HHV-6 myelitis. Because CIPS and HHV-6 myelitis require completely different strategies (i.e., discontinuation of calcineurin inhibitor or use of antiviral agents), it is important to carefully differentiate between the two possibilities.

Regarding treatment, GCV and FCN, either alone or in combination, might be preferred over cidofovir because the ability of the latter drug to penetrate the blood–brain barrier in humans is controversial [40]. It is unknown which one of these drugs (i.e., GCV and GCN) provides better treatment, as no study has been performed to define the specific type, dose, or duration of ideal antiviral therapy. We chose antivirals in accordance with side effect profiles of each drug; GCV poses an additional risk of hematological toxicity, whereas FNC is associated with risks such as renal toxicity and complications from catheter-related deep vein thrombosis.

Although none of the patients with typical myelitis symptoms failed to undergo lumbar puncture, four patients with similar symptoms without HHV-6 PCR analysis of plasma and CSF were identified before 2009 (i.e., around the time when the first HHV-6 myelitis diagnosis was made). Since all four patients had symptoms of segmental bilateral pain, pruritus, autonomic nerve disorder (e.g., hyperhidrosis and sinus tachycardia attacks), and bladder–rectal disturbances, which developed around the time of engraftment (day 15–21), they all experienced PIR and were started on steroids before onset. These symptoms appeared to be more severe than those observed in the present five cases. Since they did not receive FCN or GCV at an appropriate timing, these symptoms might reflect the natural history of HHV-6 myelitis.

In conclusion, myelitis occurring shortly after CBT is not rare. Onset begins with pruritus or pain, and autonomic symptoms and bladder–rectal disturbance could occur. We suspect that CIPS-like pain shortly after CBT in some cases might be associated with reactivation of HHV-6. For cases in which HHV-6 myelitis is suspected, DNA PCR analysis of CSF and immediate administration of anti-viral drugs are needed. In addition, methods to effectively prevent HHV-6 reactivation should be established.

Compliance with ethical standards

Conflict of interest The authors report no financial relationship with any company that has a direct financial interest in the subject matter or products discussed in the submitted manuscript, or with any company that produces a competing product.

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