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Case Report

Fatal veno-occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS) developing after high-dose chemotherapy combined with autologous peripheral blood stem cell transplantation for recurrent malignant lymphoma: report of a case

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Abstract: The patient, a 64-year-old man, was diagnosed as having diffuse large B cell lymphoma (DLBCL) in June 2013. Complete remission (CR) was achieved after eight cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone) therapy. The disease recurred in October 2014, and CR was achieved again after three cycles of R-GDP (rituximab, gemcitabine, cisplatin, and dexamethasone) therapy. Autologous peripheral blood stem cells (auto-PBSC) were collected after a single cycle of R-ESHAP (rituximab, etoposide, methylprednisolone, cytarabine and cisplatin) therapy. In March 2015, autologous peripheral blood stem cell transplantation (auto-PBSCT) was performed after pre-treatment with MCVAC (ranimustine, cytarabine, etoposide and cyclophosphamide) regimens. The patient's body weight gradually increased post-transplantation, along with progressively worsening liver function. On day 12, a clinical diagnosis of veno-occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS) was made. Administration of thrombomodulin a (rTM) and a glycyrrhizin-containing preparation (Stronger Neo-Minophagen C [SNMC]), plasma exchange (PE), treatment with ursodeoxycholic acid (UDCA), and steroid pulse therapy failed to afford any improvement and the patient died of hepatic failure on day 19 post-transplantation. A postmortem examination was performed, which confirmed the diagnosis of VOD/SOS. This report documents a fatal and rare case of VOD/SOS developing after auto-PBSCT.

Keywords: Malignant lymphoma, high-dose chemotherapy combined with autologous peripheral blood stem cell transplantation, veno-occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS)

Introduction

The pathophysiology of veno-occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS) still remains obscure and there are no established preventive or curative treatments. While defibrotide has been reported from overseas to be effective for this disorder, this drug is not yet approved in Japan. VOD/SOS occurring after allogeneic hematopoietic stem cell transplantation has been sporadically documented, however, development of this serious disorder after autologous hematopoietic stem cell transplantation has been relatively rarely reported. While the pretreatment regimen employed prior to transplantation has been suggested as a risk factor, a variety of other factors have also been implicated; multiple factors are generally recognized to be involved. The case presented herein is the first reported case with VOD/SOS showing a causal association with MCVAC (ranimustine, cytarabine, etoposide and cyclophosphamide [CY]) chemotherapy. In this case, CY or ranimustine was suspected as the causative factor. The diagnosis of this disorder in the clinical practice setting continues to be based

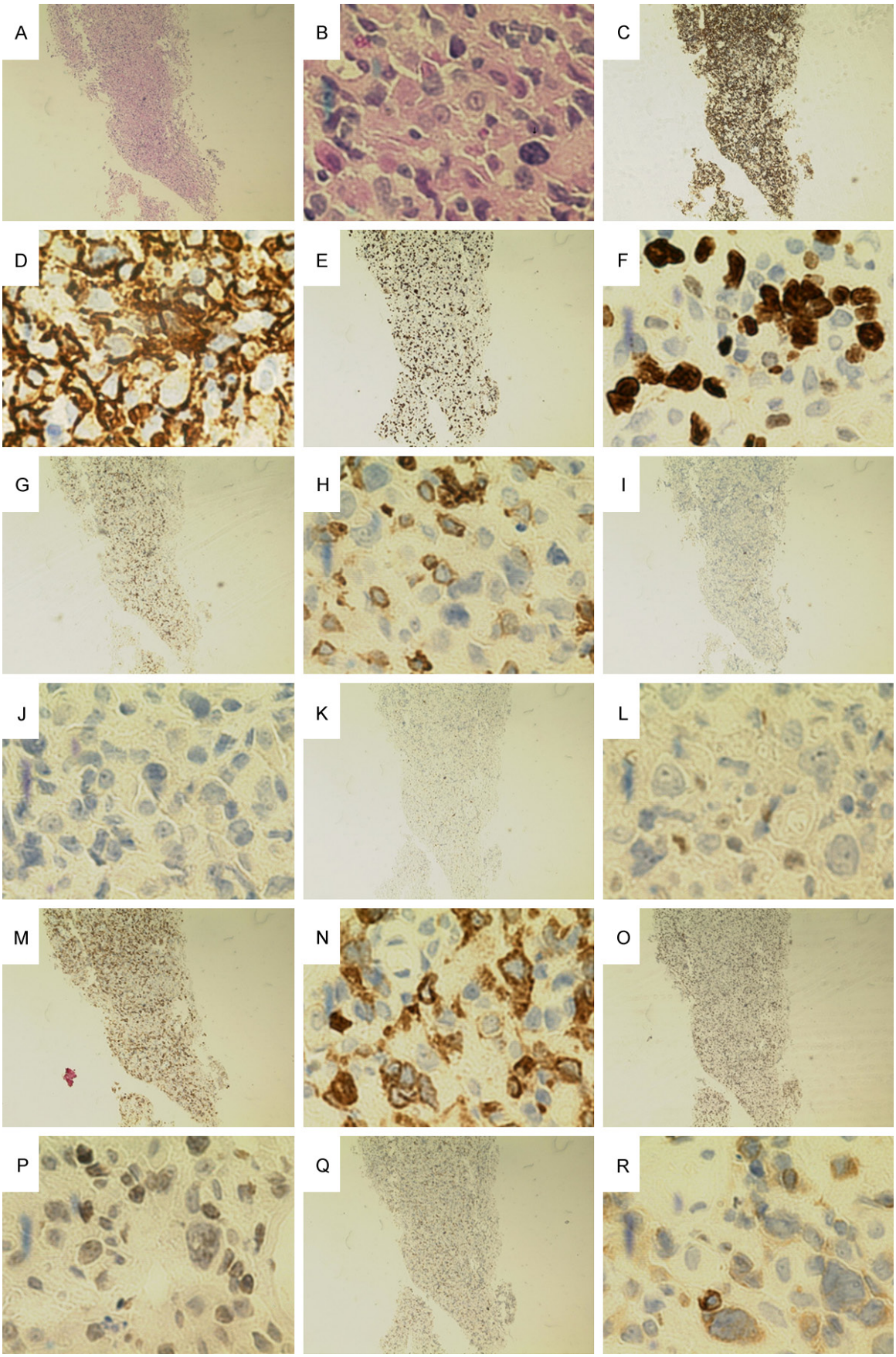
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Figure 1. Right axillary lymph node biopsy. A. (Hematoxylin and eosin [HE] ×40): Diffuse infiltrate of atypical lymphocytes with prominent large nucleoli. B. (HE ×600): Diffuse infiltrate of atypical lymphocytes with prominent large nucleoli. C. (CD20 ×40): Positive. D. (CD20 ×600): Positive. E. (Ki-67 ×40): Highly positive. F. (Ki-67 ×600): Highly positive. G. (CD5 ×40): Negative. H. (CD5 ×600): Negative. I. (CD10 ×40): Negative. J. (CD10 ×600): Negative. K. (Cyclin-D1 ×40): Negative. L. (Cyclin-D1 ×600): Negative. M. (CD79a ×40): Positive. N. (CD79a ×600): Positive. O. (Latent membrane protein-1 [LMP-1] ×40): Negative. P. (LMP-1 ×600): Negative. Q. (B-cell lymphoma 2 [bcl-2] ×40): Weakly positive. R. (bcl-2 ×600): Weakly positive.

Table 1. Laboratory findings on transferred admission to this hospital

CBC		Biochemistry		Immuno-Serological findings	
WBC	2200/μL↓	T.P	5.5 g/dL↓	IgG	254 mg/dL↓
Myelo	1.0%↑	Alb	4.0 g/dL	IgA	88 mg/dL↓
Band	13.0%↑	AST	25 IU/L	IgM	29 mg/dL↓
Seg	46.0%	ALT	20 IU/L	Antinuclear antibodies: Negative	
Ly	20.0%↓	LDH	378 IU/L↑	sIL-2R	622 U/mL↑
Mono	17.0%↑	ALP	101 IU/L	Anti-HTLV-1 antibody: Negative	
Eo	1.5%	γ-GTP	33 IU/L	Anti-HIV antibody: Negative	
Ba	1.0%	T-Bil	0.4 mg/dL	IgM-HA Negative	
ERB	0.5%↑	BUN	13 mg/dL	HBsAg Negative	
RBC	243×10^4/μL↓	Cr	0.90 mg/dL	HBsAb Negative	
Hb	8.5 g/dL↓	CRP	≤ 0.3 mg/dL	HBcAg Negative	
Hct	25.0%↓	Ferritin	1732.0 ng/mL↑	HBcAb Negative	
MCV	102.9 fl↑			HBeAg Negative	
MCH	35.2 pg			HBeAb Negative	
Plt	18.1×10^4/μL			HCVAb Negative	
Reti	8.3%↑				
Coagulation profile		Urinalysis			
PT	≥ 100%	No abnormality			
APTT	25.0 sec				
Fbg	329 mg/dL				
FDP	≤ 5.0 μg/mL				
DD	0.59 μg/mL				
AT3	109%				

Decreased white blood cell count, anemia, elevated serum LDH, elevated serum ferritin, slightly increased serum soluble IL-2 receptor, and polyclonal hypogammaglobulinemia were noted. Tests for the hepatitis markers were all negative. WBC, white blood cell; Myelo, myelocyte; seg, segmented neutrophils; Ly, lymphocyte; Mono, monocyte; Eo, eosinophil; Ba, basophil; ERB, erythroblast; RBC, red blood cell; Hb, hemoglobin; Ht, hematocrit; MCV, mean corpuscular cell volume; MCH, mean corpuscular cell hemoglobin; Plt, platelet; Reti, reticulocyte; PT, prothrombin time; APTT, activated partial thromboplastin time; Fbg, fibrinogen; FDP, fibrinogen degradation products; DD, D-dimers; AT III, antithrombin III; T.P, total protein; Alb, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; γ-GTP, γ-guanosine triphosphate; T-Bil, total bilirubin; BUN, blood urea nitrogen; Cr, creatinine; Ca; calcium; CRP, C-reactive protein; IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M; sIL-2R, soluble interleukin-2 receptor; HTLV-1, human T cell leukemia virus-1; HIV, human immunodeficiency virus; IgM-HA, immunoglobulin M-hepatitis A; HBsAg, hepatitis B surface antigen; HBsAb, antibody to hepatitis B surface antigen; HBcAg, hepatitis B core antigen; HBcAb, antibody to hepatitis B core antigen; HBeAg, hepatitis B antigen; HBeAb, antibody to hepatitis B antigen; HCVAb, antibody to hepatitis C virus.

essentially on clinical diagnostic criteria. The precise incidence of cases with a pathologically established diagnosis of VOD/SOS remains unclear due to the rarity of cases in which the diagnosis is made by antemortem liver biopsy. The mortality may exceed 90% if the disease progresses to a serious stage. Clarification of the pathophysiology of VOD/SOS and establishment of preventive and treatment measures are urgently needed.

Case report

The patient, a 64-year-old man, was diagnosed as having diffuse large B cell lymphoma (DLBCL) and received high-dose chemotherapy with

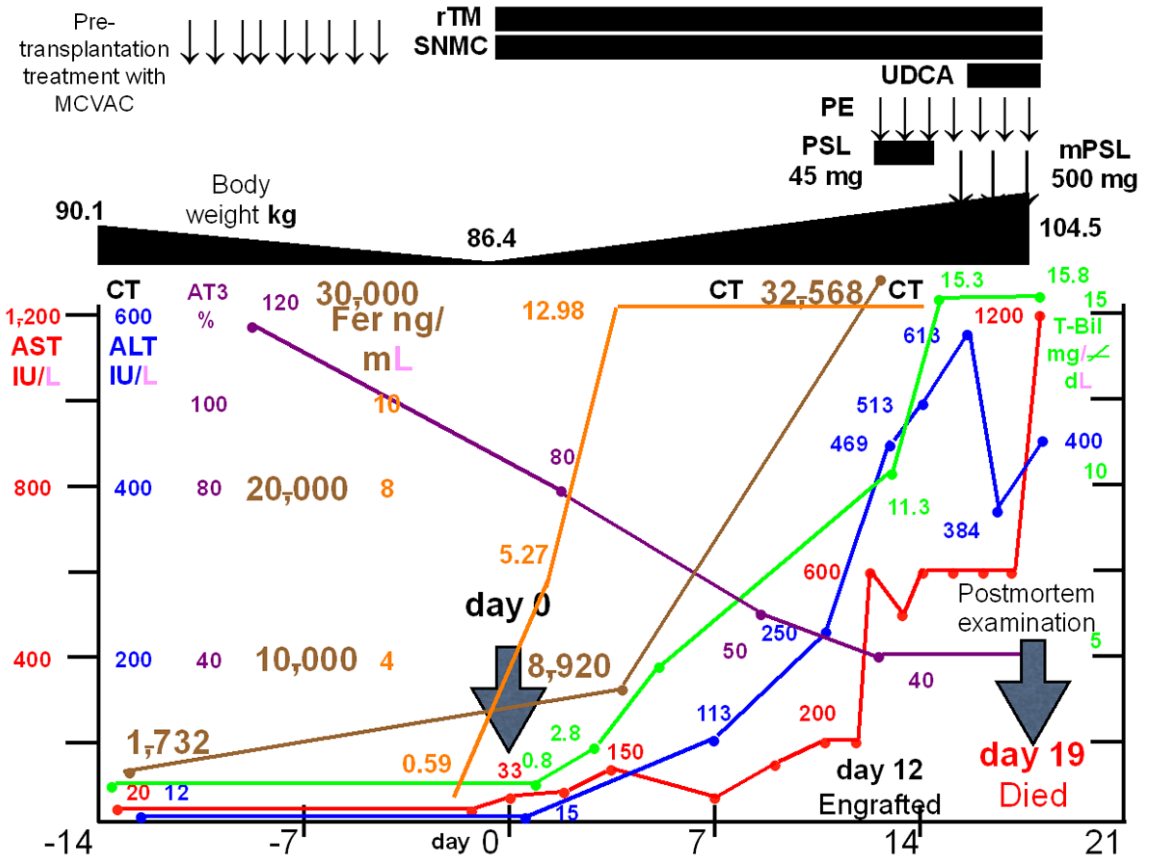

Figure 2. Clinical course. Auto-PBSCT was performed after treatment with the MCVAC regimen. The body weight of the patient gradually increased post-transplantation, along with progressive worsening of the liver function. CT performed on day 6 post-transplantation revealed modest ascites. A repeat CT on day 12 revealed worsening of the ascites and pleural effusion. We diagnosed the patient as having the severe form of VOD/SOS. Despite treatment with rTM and a glycyrrhizin-containing preparation (SNMC), PE, administration of UDCA and steroid pulse therapy, the patient remained unresponsive and died of hepatic failure on day 19 post-transplantation.

concomitant autologous peripheral blood stem cell transplantation (auto-PBSCT). The past history and family history were noncontributory.

The present illness

The patient first visited a clinic in his neighborhood when he became aware of swelling in the right axillary region in June 2013. A lymph node biopsy performed at the clinic led to the diagnosis of DLBCL (**Figure 1A-R**). The disease was of clinical stage IIIA and the Revised-International Prognostic Index (R-IPI) was poor-risk (age, elevated lactate dehydrogenase [LDH], and stage) [1]. Beginning in November 2013, the patient was treated with 8 cycles of R-CHOP therapy (each cycle consisting of rituximab 375 mg/m^2, CY 750 mg/m^2, vincristine 1.5 mg/m^2, doxorubicin 50 mg/m^2, and prednisolone 100 mg for 5 days), and complete remission (CR: 1st CR) was confirmed in May 2014. In October 2014, an ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET-CT) revealed increased uptake in the lungs, right axilla and bones, and the patient was diagnosed as having disease recurrence (data not shown). The patient was then treated with 3 cycles of R-GDP therapy (rituximab 375 mg/m^2 on day 1, dexamethasone 40 mg/body on days 1 to 4, gemcitabine 1000 mg/m^2 on days 1 and 8, and cisplatin 75 mg/m^2 on day 1), which again led to CR (2nd CR). The patient was referred here and admitted to this hospital in February 2015 for auto-PBSCT.

Status on admission

There was no abnormality on physical examination, except for pallor of the palpebral conjunctiva.

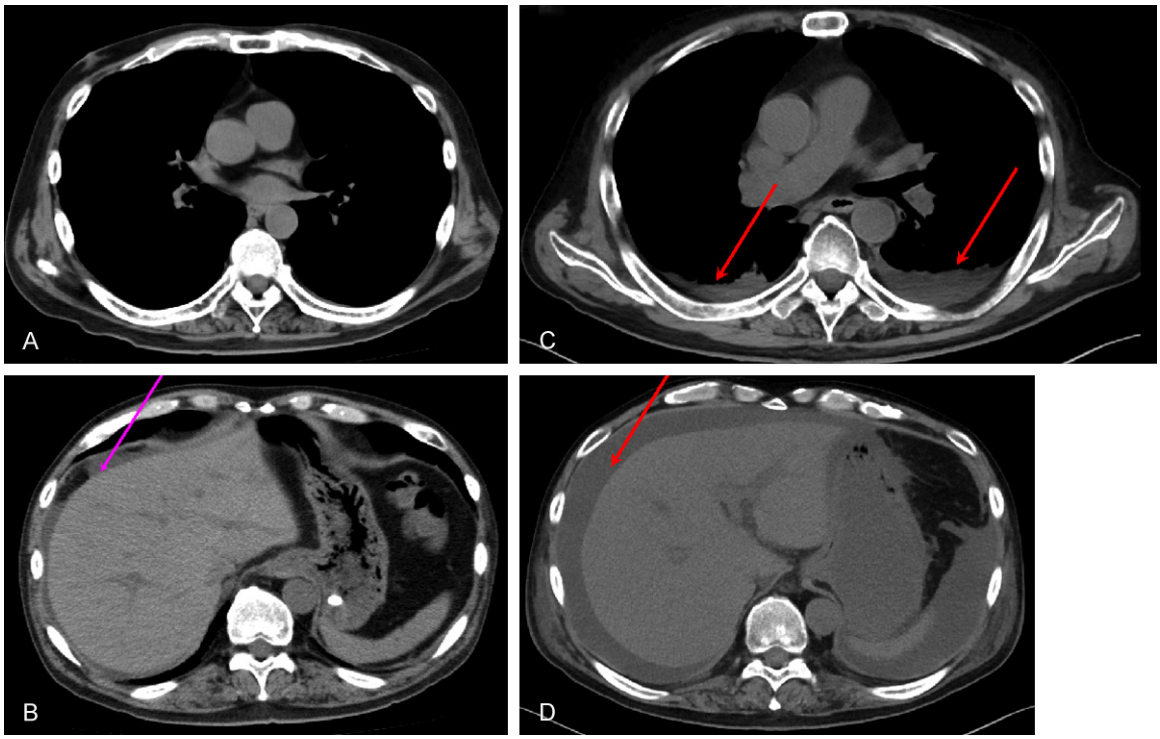

Figure 3. CT. A. (day 6): No pleural effusion. B. (day 6): Modest ascites. C. (day 12): Bilateral pleural effusion. D. (day 12): Worsening of the ascites. MCVAC therapy, ranimustine, cytarabine, etoposide, cyclophosphamide; rTM, thrombomodulin α; SNMC, glycyrrlizin-containing preparation; UDCA, ursodeoxycholic acid; PE, plasmaexchange; PSL, Prednisolone; mPSL, methylprednisolone; CT, computed Tomography; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AT3, antithrombin 3; Fer, ferritin; Y-Bil, total bilirubin.

As seen in **Table 1**, laboratory examinations revealed decreased white blood cell count, anemia, elevated serum LDH levels, and elevated serum ferritin levels. There was also evidence of polyclonal hypogammaglobulinemia. The serum level of soluble interleukin-2 (IL-2) receptor was noted to be slightly increased to 622 U/mL. Tests for hepatitis markers were all negative.

Hospital course

The patient received a single cycle of R-ESHAP therapy (consisting of rituximab 375 mg/m^2 on day 1, etoposide 40 mg/m^2 on days 1 to 4, methylprednisolone 500 mg/body on days 1 to 4, cytarabine 2 g/m^2 on day 5, and cisplatin 25 mg/m^2 on days 1 to 4), and then blood was drawn to collect autologous peripheral blood stem cells (auto-PBSC) (autologous peripheral blood cluster of differentiation [CD]-34 cell count: 3.1×10^6/kg) in late February. Starting in the middle of March, the patient received pre-transplantation treatment with high-dose MCVAC chemotherapy regimens (ranimustine 250 mg/m^2 on day -9, 200 mg/m^2 on day -4, cytarabine 2 g/m^2 b.i.d. on days -8 to -5, etoposide 200 mg/m^2 b.i.d. on days -8 to -5, and CY 50 mg/kg on days -3 and -2) [2], followed in late March by auto-PBSCT (**Figure 2**). Along with loss of appetite, the patient lost weight by 3.7 kg from the start of the pretreatment (90.1 kg) to day 0 of transplantation (86.4 kg). There was no abnormality of the hepatic function. However, the body weight gradually increased post-transplantation, along with progressively worsening liver function. The patient was administered thrombomodulin α (rTM) at 380 U/kg and Stronger Neo-Minophagen C (SNMC), a glycyrrhizin-containing preparation. On day 6 post-transplantation, computed tomography (CT) performed because of worsening hepatic dysfunction revealed a modest amount of ascites (**Figure 3A** and **3B**). The patient was referred to the Department of Gastroenterology for a liver biopsy, but unfortunately, the biopsy proved infeasible. Laboratory tests for hepatitis markers remained negative (**Table 2**). Tests for markers of infections were also negative (**Table 2**). Despite consecutive daily blood transfusion,

Table 2. Laboratory findings on day 6

Immunoserological findings		Coagulation profile	
IgM-HA	Negative	PT	59%
HBsAg	Negative	APTT	35.4 sec
HBsAb	Negative	Fbg	498 mg/dL
HBcAg	Negative	FDP	15.7 μg/mL
HBcAb	Negative	DD	7.95 μg/mL
HBeAg	Negative	AT III	76%
HBeAb	Negative		
HCVAb	Negative		
CMVAg (C7-HRP)	Negative		
HSV IgM	Negative		
VZV IgM	Negative		
EBV VCA IgM	Negative		
Candida Ag	Negative		
Aspergillus Ag	Negative		
b-D-glucan	Negative		

Tests for the hepatitis and infection markers remained negative. DIC was suspected on the basis of the results of the blood coagulation tests. IgM-HA, immunoglobulin M-hepatitis A; HBsAg, hepatitis B surface antigen; HBsAb, antibody to hepatitis B surface antigen; HBcAg, hepatitis B core antigen; HBcAb, antibody to hepatitis B core antigen; HBeAg, hepatitis B antigen; HBeAb, antibody to hepatitis B antigen; HCVAb, antibody to hepatitis C virus; CMVAg, cytomegalovirus antigen; HSV IgM, immunoglobulin M-herpes simplex virus; VZV IgM, immunoglobulin M-varicella-zoster virus; EBV VCA IgM, immunoglobulin M-Epstein-Barr virus; PT, prothrombin time; APTT, activated partial thromboplastin time; Fbg, fibrinogen; FDP, fibrinogen degradation products; DD, D-dimers; AT III, antithrombin III.

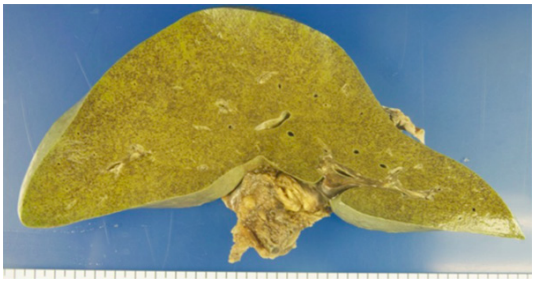

Figure 4. Gross pathologic findings of the liver. The liver weighed 1700 g and was found to be markedly yellow in color. The abdominal cavity contained 3600 mL of serosanguineous ascitic fluid.

the platelet count remained to be in the region of 1×10^4/μL, that is, it remained unresponsive to the transfusion. A diagnosis of disseminated intravascular coagulation (DIC) was made on the basis of the results of blood coagulation tests (**Table 2**). As the liver function continued to worsen, an abdominal CT was repeated again on day 12, which revealed worsening of the ascites and development of pleural effusion (**Figure 3C** and **3D**). The patient fulfilled all of the following criteria for the diagnosis of VOD/SOS: Seattle criteria [3, 4], Modified Seattle criteria [5], Baltimore criteria [6], and the criteria proposed by Corbacioglu et al. [7]; therefore, the patient was diagnosed as having VOD/SOS. As for the clinical grade, the total bilirubin (T-Bil) was 6.0 mg/dL, the serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were 167 and 184 IU/L, respectively, the weight loss was 21%, and the serum creatinine (Cr) was 3.35 mg/dL; thus the clinical rate of progression was assessed as being more severe than rapid [8]. Heparin could not be administered on account of a pronounced bleeding tendency because of a platelet count in the region of 1×10^4/μL. Graft-versus-host disease (GVHD) or hemophagocytic syndrome (HPS) as a possible complication could not be ruled out; therefore, the patient was started on treatment with prednisolone (PSL) at the dose of 45 mg/day. Plasma exchange (PE) was also undertaken because of the worsening liver function. As there was still no indication of improvement, ursodeoxycholic acid (UDCA) administration was started, with steroid pulse therapy using methylprednisolone (mPSL) at 500 mg/day for 3 days. However, the patient's clinical condition failed to improve and the patient died of hepatic failure on day 19 post-transplantation. A postmortem examination was performed; in regard to the gross pathological findings of the liver, there was conspicuous yellowish discoloration of the liver, and the organ weighed 1700 g (**Figure 4**). Microscopically, centrilobular hemorrhagic necrosis of the liver was observed (**Figure 5A** and **5B**) and the central veins were narrowed (**Figure 5C**) or indiscrete (**Figure 5D**). There was no fibrin deposition in the vicinity of the central veins (**Figure 5E**), whereas on silver-stained sections, proliferation of reticular fibers was noted around the central veins (**Figure 5E**). These findings were considered to be consistent with the features of VOD/SOS.

Discussion

We made a diagnosis of clinically serious VOD/SOS in the case reported herein, in which antemortem liver biopsy proved infeasible [3-8]. As concurrent GVHD or HPS could not be ruled out, we had no other alternative but to start the

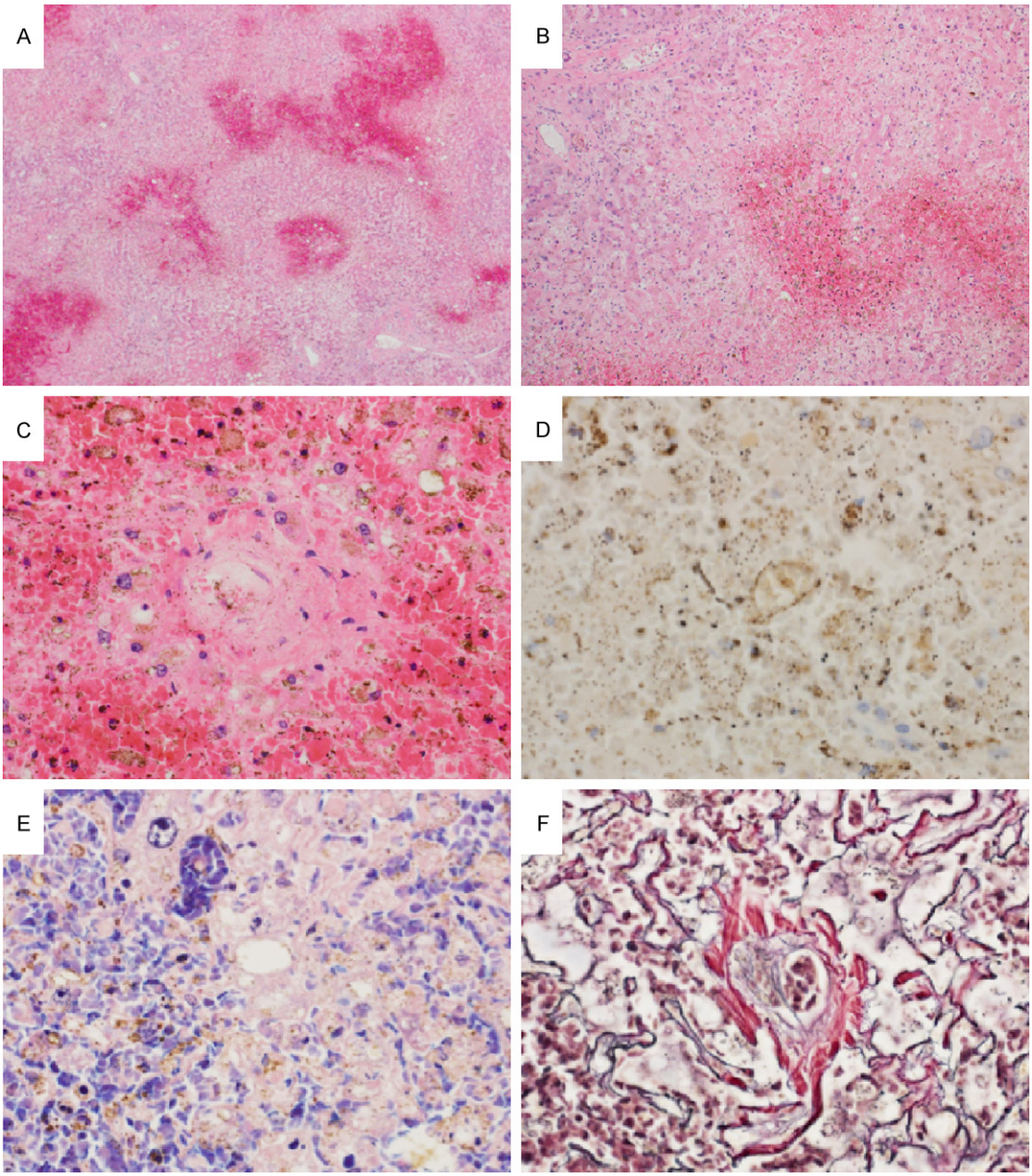

Figure 5. Microscopic findings of the liver. A. (HE ×?): Centrilobular hemorrhagic necrosis of the liver. B. (HE ×?): Centrilobular hemorrhagic necrosis of the liver. C. (HE ×?): Centrilobular hemorrhagic necrosis of the liver. The central vein is narrowed. D. (CD34: Vascular endothelium ×?): The central vein is indiscrete. E. (Phosphotungstic acid-hematoxylin [PTAH]: Fibrin ×?): There is no fibrin deposition in the central vein. F. (Silver stained ×?): Proliferation of reticular fibers is noted in the vicinity of the central vein.

patient on PSL (0.5 mg/kg) and administer steroid pulse therapy. A liver biopsy was indispensable for a definitive diagnosis in this case, however, it proved infeasible because of the unfavorable coagulation profile of the patient. It has been described, in fact, that the clinical diagnostic criteria lack certainty not only in terms of a definitive diagnosis, but also in terms of diagnosis by exclusion [9]. Therefore, transjugular liver biopsy has been recommended [9]. Doppler ultrasound (US) test is also recognized as being useful for diagnosis [10].

Table 3. Reports of cases of VOD developing after autologous transplantation

	Authors	n	Regimen	VOD %	Reference No.
1	Fernandez	44	i.v. Bu/Cy	4.6	15
2	Hanel et al.	43	Oral Bu/Cy/E	5.8	16
3	DeMagalhaes-Silverman et al.	20	oral Bu/Cy	15	17
4	Kim et al.	64	i.v. Bu/Cy/E	6.3	18
5	Copelan et al.	382	Oral Bu/Cy/E	2.9	19
6	Ballester et al.	21	oral Bu/Cy	4.7	20
7	Schiffman et al.	40	Bu/Mel/TT	23	21
8	Ulrickson et al.	78	Bu/Cy	3.8	22
9	Kato et al.	40	MCVAC	0	2
10	Kameoka et al.	30	MCVC	16	23
11	Sekiguchi et al.	50	MCVAC/MCVC	2.0	this case

The reported incidence of VOD ranged from 0 to 23%. I.V., intravenous; Bu, busulfan; Cy, cyclophosphamide; E, etoposide; Mel, melphalan; TT, thiotepa; MCVAC, ranimustine, cytarabine, etoposide, cyclophosphamide; MCVC, ranimustine, carboplatin, etoposide, cyclophosphamide.

Our patient reported herein remained unresponsive to various treatments (rTM, SNMC, UDCA, PSL 45 mg/kg, mPSL 500 mg, and PE) and died on day 19 post-transplantation. On the basis of a trial that demonstrated the efficacy of PE in combination with recombinant tissue-type plasminogen activator (rt–PA) treatment for VOD/SOS [25], we performed PE in the present case; however, the therapeutic response was transient. Furthermore, heparin was contraindicated in this case because of a marked bleeding tendency.

The reported incidence of VOD/SOS following hematopoietic stem cell transplantation varies widely, ranging from 5 to 60% [11, 12], although it is generally lower after autologous transplantation (3.1 to 4%), as compared to allogeneic transplantation (8.9 to 11%) [13, 14]. Some immunological mechanisms have been implicated in the increased frequency of this disease in patients who have received allogeneic transplantation [13, 14]. It is noteworthy that the reported incidence varies remarkably from 0 to 23% even when cases of autologous transplantation alone are considered (**Table 3**).

In one case series, the severity of VOD/SOS was mild in 12% of cases, moderate in 26% and severe in 15% of cases, and the 100-day mortality rates post-transplantation in the three groups were 9%, 23% and 98% in the three groups, respectively [11]; thus, patients with severe VOD/SOS carry an extremely grave prognosis. This underscores the importance of urgent establishment of effective preventive and treatment measures.

In regard to prevention and treatment, there is no established treatment at present, and supportive treatment remains the mainstay [24]. Overseas clinical trials have reported a rather high efficacy of defibrotide [24], however, this drug is not yet approved in Japan and its use at present remains restricted solely to certain clinical trial facilities. Early availability of defibrotide in Japan as well is strongly sought.

The present case is the first to be reported, to the best of our knowledge, of VOD/SOS developing in a patient who received MCVAC chemotherapy as pre-treatment prior to stem cell transplantation. CY or ranimustine was suspected as the causative factor.

In the clinical practice setting, diagnosis is primarily based on the clinical findings and cases and facilities that allow diagnostic exploration up to liver biopsy are fairly limited. Eventually, the precise frequency and severity of VOD/SOS encountered in the clinical practice setting are unclear and vary among reports in the literature (**Table 3**). A detailed review and assessments of further accumulated cases with a proven pathologically established diagnosis by liver biopsy are considered to be of vital importance.

Disclosure of conflict of interest

None.

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References

[1] Sehn LH, Berry B, Chhanabhai M, Fitzgerald C, Gill K, Hoskins P, Klasa R, Savage KJ, Shenkier

T, Sutherland J, Gascoyne RD, Connors JM. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. Blood 2007; 109: 1857-61.

[2] Kato J, Mori T, Yokoyama K, Tsukada Y, Ueda T, Shimizu T, Okamoto S. Safety and efficacy of high-dose ranimustine, cytarabine, etoposide and CY (MCVAC) regimen followed by autologous peripheral blood stem cell transplantation for high-risk diffuse large B-cell lymphoma. Bone Marrow Transplant 2011; 46: 923-8.

[3] McDonald GB, Sharma P, Matthews DE, Shulman HM, Thomas ED. Venocclusive disease of the liver after bone marrow transplantation: diagnosis, incidence, and predisposing factors. Hepatology 1984; 4: 116-22.

[4] Dulley FL, Kanfer EJ, Appelbaum FR, Amos D, Hill RS, Buckner CD, Shulman HM, McDonald GB, Thomas ED. Venocclusive disease of the liver after chemoradiotherapy and autologous bone marrow transplantation. Transplantation 1987; 43: 870-3.

[5] Shulman HM, Hinterberger W. Hepatic veno-occlusive disease--liver toxicity syndrome after bone marrow transplantation. Bone Marrow Transplant 1992; 10: 197-214.

[6] Jones RJ, Lee KS, Beschorner WE, Vogel VG, Grochow LB, Braine HG, Vogelsang GB, Sensenbrenner LL, Santos GW, Saral R. Venoocclusive disease of the liver following bone marrow transplantation. Transplantation 1987; 44: 778-83.

[7] Corbacioglu S, Cesaro S, Faraci M, Valteau-Couanet D, Gruhn B, Rovelli A, Boelens JJ, Hewitt A, Schrum J, Schulz AS, Müller I, Stein J, Wynn R, Greil J, Sykora KW, Matthes-Martin S, Führer M, O'Meara A, Toporski J, Sedlacek P, Schlegel PG, Ehlert K, Fasth A, Winiarski J, Arvidson J, Mauz-Körholz C, Ozsahin H, Schrauder A, Bader P, Massaro J, D'Agostino R, Hoyle M, Iacobelli M, Debatin KM, Peters C, Dini G. Defibrotide for prophylaxis of hepatic veno-occlusive disease in paediatric haemopoietic stem-cell transplantation: an open-label, phase 3, randomised controlled trial. Lancet 2012; 379: 1301-9.

[8] Fan CQ, Crawford JM. Sinusoidal obstruction syndrome (hepatic veno-occlusive disease). J Clin Exp Hepatol 2014; 4: 332-46.

[9] Carreras E, Grañena A, Navasa M, Bruguera M, Marco V, Sierra J, Tassies MD, García-Pagán JC, Martí JM, Bosch J, et al. On the reliability of clinical criteria for the diagnosis of hepatic veno-occlusive disease. Ann Hematol 1993; 66: 77-80.

[10] Lassau N, Auperin A, Leclere J, Bennaceur A, Valteau-Couanet D, Hartmann O. Prognostic value of doppler-ultrasonography in hepatic veno-occlusive disease. Transplantation 2002; 74: 60-6.

[11] McDonald GB, Hinds MS, Fisher LD, Schoch HG, Wolford JL, Banaji M, Hardin BJ, Shulman HM, Clift RA. Veno-occlusive disease of the liver and multiorgan failure after bone marrow transplantation: a cohort study of 355 patients. Ann Intern Med 1993; 118: 255-67.

[12] Hogan WJ, Maris M, Storer B, Sandmaier BM, Maloney DG, Schoch HG, Woolfrey AE, Shulman HM, Storb R, McDonald GB. Hepatic injury after nonmyeloablative conditioning followed by allogeneic hematopoietic cell transplantation: a study of 193 patients. Blood 2004; 103: 78-84.

[13] Carreras E, Bertz H, Arcese W, Vernant JP, Tomás JF, Hagglund H, Bandini G, Esperou H, Russell J, de la Rubia J, Di Girolamo G, Demuynck H, Hartmann O, Clausen J, Ruutu T, Leblond V, Iriondo A, Bosi A, Ben-Bassat I, Koza V, Gratwohl A, Apperley JF. Incidence and outcome of hepatic veno-occlusive disease after blood or marrow transplantation: a prospective cohort study of the European Group for Blood and Marrow Transplantation. European Group for Blood and Marrow Transplantation Chronic Leukemia Working Party. Blood 1998; 92: 3599-604.

[14] Ayash LJ, Hunt M, Antman K, Nadler L, Wheeler C, Takvorian T, Elias A, Antin JH, Greenough T, Eder JP. Hepatic venoocclusive disease in autologous bone marrow transplantation of solid tumors and lymphomas. J Clin Oncol 1990; 8: 1699-706.

[15] Fernandez H. The use of intravenous busulfan and cyclophosphamide as a conditioning regimen for non-Hodgkin's lymphoma. ASBMT/CIBMTR Tandem Meetings. Honolulu: Hawaii; 2006.

[16] Hänel M, Kröger N, Sonnenberg S, Bornhäuser M, Krüger W, Kroschinsky F, Hänel A, Metzner B, Birkmann J, Schmid B, Hoffknecht MM, Fiedler F, Ehninger G, Zander AR. Busulfan, cyclophosphamide, and etoposide as high-dose conditioning regimen in patients with malignant lymphoma. Ann Hematol 2002; 81: 96-102.

[17] de Magalhaes-Silverman M, Lister J, Rybka W, Wilson J, Ball E. Busulfan and cyclophosphamide (BU/CY2) as preparative regimen for patients with lymphoma. Bone Marrow Transplant 1997; 19: 777-81.

[18] Kim JG, Sohn SK, Chae YS, Yang DH, Lee JJ, Kim HJ, Shin HJ, Jung JS, Kim WS, Kim DH, Suh C, Kim SJ, Eom HS, Bae SH. Multicenter study of intravenous busulfan, cyclophosphamide, and etoposide (i.v. Bu/Cy/E) as conditioning regimen for autologous stem cell transplanta-

tion in patients with non-Hodgkin's lymphoma. Bone Marrow Transplant 2007; 40: 919-24.
[19] Copelan EA, Penza SL, Pohlman B, Avalos BR, Goormastic M, Andresen SW, Kalaycio M, Bechtel TP, Scholl MD, Elder PJ, Ezzone SA, O'Donnell LC, Tighe MB, Risley GL, Young DC, Bolwell BJ. Autotransplantation following busulfan, etoposide and cyclophosphamide in patients with non-Hodgkin's lymphoma. Bone Marrow Transplant 2000; 25: 1243-8.
[20] Ballester OF, Agaliotis DP, Hiemenz JW, Janssen WE, Fields KK, Zorksy PE, Goldstein SC, Perkins JB, Elfenbein GJ. Phase I-II study of high-dose busulfan and cyclophosphamide followed by autologous peripheral blood stem cell transplantation for hematological malignancies: toxicities and hematopoietic recovery. Bone Marrow Transplant 1996; 18: 9-14.
[21] Schiffman KS, Bensinger WI, Appelbaum FR, Rowley S, Lilleby K, Clift RA, Weaver CH, Demirer T, Sanders JE, Petersdorf S, Gooley T, Weiden P, Zuckerman N, Montgomery P, Maziarz R, Klarnet JP, Rivkin S, Trueblood K, Storb R, Holmberg L, Buckner CD. Phase II study of high-dose busulfan, melphalan and thiotepa with autologous peripheral blood stem cell support in patients with malignant disease. Bone Marrow Transplant 1996; 17: 943-50.
[22] Ulrickson M, Aldridge J, Kim HT, Hochberg EP, Hammerman P, Dube C, Attar E, Ballen KK, Dey BR, McAfee SL, Spitzer TR, Chen YB. Busulfan and cyclophosphamide (Bu/Cy) as a preparative regimen for autologous stem cell transplantation in patients with non-Hodgkin lymphoma: a single-institution experience. Biol Blood Marrow Transplant 2009; 15: 1447-54.
[23] Kameoka Y, Takahashi N, Ishizawa K, Kato Y, Ito J, Sasaki O, Murai K, Noji H, Hirokawa M, Tajima K, Shichishima T, Ishida Y, Harigae H, Sawada K. Safety and feasibility of high-dose ranimustine (MCNU), carboplatin, etoposide, and cyclophosphamide (MCVC) therapy followed by autologous stem cell transplantation for malignant lymphoma. Int J Hematol 2012; 96: 624-30.
[24] Dignan FL, Wynn RF, Hadzic N, Karani J, Quaglia A, Pagliuca A, Veys P, Potter MN; Haemato-oncology Task Force of British Committee for Standards in Haematology; British Society for Blood and Marrow Transplantation. BCSH/BSBMT guideline: diagnosis and management of veno-occlusive disease (sinusoidal obstruction syndrome) following haematopoietic stem cell transplantation. Br J Haematol 2013; 163: 444-57.
[25] Espigado I, Rodríguez JM, Parody R, Carmona M, Digón J, Olloqui E. Reversal of severe hepatic veno-occlusive disease by combined plasma exchange and rt-PA treatment. Bone Marrow Transplant 1995; 16: 313-6.