Budd–Chiari syndrome associated with hypereosinophilic syndrome treated by deceased-donor liver transplantation: A Case Report

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Declaration of interest: none

Keywords:

liver transplantation, Budd–Chiari syndrome, hypereosinophilic syndrome, veno-venous bypass

Highlights:

- Budd-Chiari syndrome (BCS) associated with hepereosinophilic syndrome (HES)
- Diagnosis and treatment strategy for BCS associated with HES
- First case report of successful liver transplantation for BCS associated with HES

Abstract

Introduction: Budd–Chiari syndrome (BCS) associated with hypereosinophilic syndrome (HES) is very rare, and only a few reports have described its treatment. Furthermore, no report to date has described the performance of liver transplantation for the treatment of BCS associated with HES. We herein describe a 54-year-old man who underwent deceased-donor liver transplantation (DDLT) for treatment of BCS associated with HES.

Case: A 54-year-old man was found to have an increased eosinophil count during a medical check-up. After exclusion of hematopoietic neoplastic diseases and secondary eosinophilia, idiopathic hypereosinophilia was diagnosed. Oral prednisolone was administered to the patient, and his eosinophil count immediately decreased to a normal level. He had an uneventful course without complications for 11 months but then presented with bloating and malaise. Imaging studies including ultrasonography, enhanced computed tomography, and angiography revealed BCS associated with HES. Transjugular intrahepatic portosystemic shunt (TIPS) failed because of complete obstruction of the hepatic veins. Therefore, the patient was introduced to our hospital for liver transplantation. DDLT was performed with veno-venous bypass 1 month after the patient was placed on the DDLT waiting list. The explanted hepatic veins were completely occluded and organized. The patient's eosinophil count was maintained at a normal level with prednisolone treatment after DDLT.

Conclusion: Liver transplantation can be a treatment option for BCS associated with HES if

neoplastic diseases and secondary eosinophilia have been excluded. Life-long oral steroid therapy is required to control HES even after liver transplantation.

Introduction

The diagnostic criteria for hypereosinophilia and hypereosinophilic syndrome (HES) were reported by Peter et al. [1] and are shown in Table 1. HES is defined as an increase in the peripheral blood eosinophil count (>1,500/μL) with resultant dysfunction of various organ systems (including the cardiac, respiratory, skin, gastrointestinal, and neurological systems) and the development of deep venous thrombosis. However, HES is a very rare disease; the age-adjusted incidence rate reportedly ranges from 0.036 to 6.300 per 100,000 population [2, 3].

Previous systematic reviews have revealed several effective treatment agents for HES, including steroids, hydroxyurea, interferon-α, cyclosporine, imatinib, anti-interleukin-5 antibody, and others [4,5]. In those reports, approximately 80% of patients were treated with corticosteroids as the initial therapy. Although the appropriate dose has not been standardized, one study indicated that the median maintenance dosage was 10 mg/day of prednisolone (PSL), the treatment duration ranged from 2 months to 20 years, and the treatment response rate was 85% [6].

Even fewer reports have described Budd–Chiari syndrome (BCS) associated with HES [7-14], although some reports have stated that HES caused thrombosis in the portal or hepatic veins [6,15,16]. The treatment described in most previous reports of BCS associated with HES was medical therapy, such as steroids, anticoagulants, unfractionated heparin, and antithrombin-III; few reports have described surgical treatments or interventions. In particular,

no reports to date have described liver transplantation as treatment for BCS associated with HES. We herein report the first case of deceased-donor liver transplantation (DDLT) for treatment of BCS associated with HES.

Case Presentation

A previously healthy 54-year-old man was found to have an increased white blood cell count during a medical check-up. He had never experienced an allergic reaction, parasitic infection, or drug toxicity and had no significant family history. The laboratory data on the first medical visit are shown in Table 2. These data showed an increased white blood cell count of 29,000/ μL with 75% eosinophils (total eosinophil count: 21,700/ μL). Viral markers for hepatitis B and C and anti-mitochondria antibody were negative, while serum immunoglobulin E was elevated. Ultrasound, enhanced computed tomography, and gastrointestinal endoscopic examinations revealed no abnormalities. Bone marrow biopsy showed no malignant cells; however, an excess of eosinophils was present (eosinophils, 55.4%; promyelocytes, 4.6%; myelocytes, 16.6%; metamyelocytes, 13.4%; stab cells, 11.6%; segmental cells, 9.2%). Chromosome analysis demonstrated a normal karyotype (46,XY), and gene mutation tests for hematopoietic malignancies such as *BCR/ABL* and *FIP1L1-PDGFRA* were negative. Moreover, other possible neoplastic diseases and causes of responsive eosinophilia, including allergic and parasitic diseases, were excluded. Finally, idiopathic hypereosinophilia was diagnosed, and

oral PSL was administered at 10 mg/day. The eosinophil count decreased to a normal level immediately after initiating treatment.

Although the patient had an uneventful course without complications for 11 months, he subsequently presented with bloating and malaise. Table 3 shows the laboratory test results on admission, which showed hepatic dysfunction. Imaging studies, including ultrasound and enhanced computed tomography, revealed BCS; an angiographic imaging study confirmed the diagnosis (Figure 1a–c). Finally, the patient was diagnosed with BCS associated with HES. Transjugular intrahepatic portosystemic shunt (TIPS) failed because of complete obstruction of the hepatic veins. Because thrombosis was detected in the portal vein and superior mesenteric vein, antithrombin-III concentrate and danaparoid were administered to the patient as anticoagulant therapy. The thrombi disappeared 2 weeks later, but the hepatic vein obstruction remained. Therefore, the patient was referred to our hospital for liver transplantation. After the pre-transplant evaluation, during which hematopoietic malignancies were excluded, the patient was placed on the DDLT waiting list.

One month after being listed, the patient underwent DDLT by inferior vena cava replacement with veno-venous bypass to completely exchange the damaged native inferior vena cava and hepatic veins. The total operation time was 10 h 49 min (on-pump: 1 h 32 min), and the total blood loss was 21,496 ml. The immunosuppression regimen was tacrolimus and a steroid as shown in Figure 2.

The patient's clinical course is shown in Figure 2. On postoperative day (POD) 1, hematoma evacuation was required because compression of the portal vein disturbed the portal flow. Beginning on POD 2, heparin was administered to prevent thrombosis. On POD 39, steroid pulse therapy was begun to treat liver biopsy-proven acute cellular rejection. On POD 59, the patient was discharged from the hospital with stable liver function and good vascular flow. Notably, his eosinophil count continuously remained within the normal range during his hospital stay and outpatient clinic follow-up.

We consulted with our hematologist preoperatively regarding the post-transplant steroid therapy. Because our initial immunosuppressive steroid dose in liver transplantation was higher than the dose required to control the HES, the steroid was administered postoperatively according to our liver transplantation immunosuppressant tapering protocol, and 15 mg of PSL was his daily steroid dose at the time of hospital discharge.

Pathological findings

Figure 3 shows the macroscopic findings of the explanted liver specimens (Figure 3a, b) and additional resected tissue around the hepatic veins (Figure 3c). The explanted liver specimen was strongly congested. Moreover, the hepatic veins were completely occluded and organized, and the lumens of the hepatic veins could not be found.

Figure 4 shows the histological findings of the hepatic parenchyma (Figure 4a, b) and hepatic

veins (Figure 4c, d). The hepatic parenchymal region exhibited congestion, bleeding surrounding central veins, dislodgment of hepatic cells, and dilation of sinusoids. These findings were consistent with the change of BCS. An organized thrombus-like formation filled the lumen of the hepatic vein, and the markedly thickened vascular tunica media contained infiltration of chronic inflammatory cells, including plasmacytes, lymphocytes, and histiocytes. Eosinophils were not found around the hepatic veins.

Discussion

To the best of our knowledge, this is the first report of DDLT for treatment of BCS associated with HES. This case had two important findings. First, it showed that liver transplantation can be a treatment option for patients with BCS associated with HES if neoplasia and other diseases that cause responsive eosinophilia are excluded and eosinophilia is controlled. Second, in patients with complete obstruction of the hepatic veins, BCS associated with HES might be difficult to treat with TIPS, anticoagulant therapy, and other medical therapies.

Before DDLT, we considered that it was very important to judge the patient's eligibility for liver transplantation. Chusid et al. [17] proposed diagnostic criteria for HES, and Peter et al. [1] modified these criteria more clinically as shown in Table 1. Based on these diagnostic criteria, we examined our patient for various possible etiologies including parasitic and allergic disease, malignant disease, collagen disease, drugs, dysfunction of chronic myeloid leukemia

genes such as *BCR/ABL* and *FIPL1-PDGFRA*, and bone marrow disease. Although a previous report showed that myeloproliferative syndrome accounted for 45% of all cases of HES [18], the details of the myeloproliferative diseases were not described. Our patient was diagnosed with idiopathic HES because we found no specific etiologies. Moreover, his eosinophil count was well-controlled by oral PSL except 2 months. Therefore, we finally verified his eligibility for liver transplantation.

How HES causes BCS remains unclear. Previous studies have shown that deep thrombotic complications of HES, including portal vein thrombosis or hepatic vein obstruction, occur in about 10% to 25% of patients [4,7,15]. However, little is known about the association between BCS and HES [7-14]. Table 4 summarizes previously reported cases of BCS associated with HES. The main treatments in those reports were medications including steroids, heparin, and anticoagulant agents. Although a few reports have described surgical treatment, none have mentioned liver transplantation. Because TIPS can be an effective treatment for BCS [19-21], we attempted TIPS for our patient, but the procedure was unsuccessful. We thus concluded that the patient required a liver transplantation. Because the explanted hepatic veins were completely occluded and organized, our patient could not be treated with medical therapy, including TIPS and anticoagulant therapy.

The mechanism of organ or vascular injury is associated with cationic proteins, peroxidase, and eosinophil-derived neurotoxin released by eosinophils [22-25]. This pathogenesis induces

vascular endothelial injury, which sequentially leads to a hypercoagulable state and systemic thrombosis. However, the pathogenetic mechanism underlying the specific hepatic vein injury shown in our patient remains unknown. Schwartz [22,26] reported that the eosinophil count is not always correlated with the degree of tissue infiltration. Indeed, our patient had BCS despite a normal eosinophil count. These findings indicate that even if the eosinophil count is within the normal range, such patients need to be carefully followed up in future.

Little is known about treatment after relapse and the long-term outcome of BCS associated with HES, especially in liver transplantation recipient. The current report only describes the short-term outcome; accumulation of further data will require continued follow-up in the long term.

Conclusions

We found that liver transplantation can be a treatment option for BCS associated with HES if neoplasia and other diseases that cause responsive eosinophilia are excluded and if eosinophilia is controlled. Additionally, patients with completely occluded and organized hepatic vein might not be candidates for medical therapy including TIPS and anticoagulant therapy.

Acknowledgments

The authors thank Drs. Yuka Suzuki and Yoshie Shimoyama from the Department of Pathology,

Nagoya University Hospital for assisting with the pathological diagnosis. The authors also thank Angela Morben, DVM, ELS, from Edanz Group (www.edanzediting.com/ac), for editing a draft of this manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Table 1

The diagnostic criteria for hepereosinophilia and hypereosinophilic syndrome which partial excerpted and revised of Peter's report [1]

Proposed term	Definition and criteria
Hyperesosinophilia (HE)	> 1,500 eosinophils / μ L blood on 2 examination (interval > 4 weeks) and/or tissue HE defined by the following ; 1. Percentage of eosinophils in bone mallow section exceeds 20% of all nucleated cell and/or 2. pathologist is of the opinion that tissue infiltration by eosinophils is extensive and/or 3. Marked deposition of eosinophil granule proteins is found (in the absence or presence of major tissue infiltration by eosinophils)
Hypereosinophilic syndrome (HES)	1. Criteria for peripheral blood HE fulfilled and 2. Organ damage and/or dysfunction attributable to tissue HE and 3. Exclusion of other disorders or conditions as major reason for organ damage

Table 2

The laboratory data on the first medical visit

WBC	29000	/uL	TP	7.5	g/dL	RF	33.2	IU/ml
Seg	12 (3480)	% (/uL)	Alb	3.9	g/dl	IgG	1844	mg/dl
Eos	75 (21750	% (/uL)	T-Bil	0.4	mg/dL	IgA	177	mg/dl
Baso	1 (2900)	% (/uL)	AST	38	IU/L	IgM	188	mg/dl
Mono	4 (1160)	% (/uL)	ALT	54	Iu/L	IgE	4674	mg/dl
Lymph	7 (2030)	% (/uL)	LDH	298	IU/L	C3	50.1	mg/dl
			ALP	517	IU/L	C4	11.8	mg/dl
RBC	469 x 10^4	/uL	γ GTP	136	IU/L			
Hb	14.7	/dL	ChE	241	IU/L	TSH	1.39	ng/dl
Hct	44.4	/uL	BUN	8.8	mg/dL	Free- T3	2.8	μg/dl
Plt	25.8 x 10^4	/uL	Cr	0.96	mg/dL	Free-T4	1.0	μg/dl
			Na	141	mEq/L			
PT%	71.0	%	K	4.3	mEq/L	AMA	(-)	
PT-INR	1.19		Cl	107	mEq/L	MPO-ANCA	(-)	
APTT	30	sec				PR3-ANCA	(-)	
CRP	1.4	mg/dl	CEA	2.0	ng/ml	HBs-Ag	(-)	
Glu	113	mg/dl	CA19-9	10	ng/ml	HBs-Ab	(-)	
HbA1c	6.0	%	sIL-2	1691	U/ml	HBc-Ab	(-)	
						HCV-Ab	(-)	

Table 3

The laboratory data on admission

WBC	12500	/uL	TP	6.6	g/dL	IgG	2216	mg/dl
Seg	58 (7250)	% (/uL)	Alb	2.8	g/dl	IgA	313	mg/dl
Eos	16 (2000)	% (/uL)	T-Bil	3.5	mg/dL	IgM	240	mg/dl
Baso	1 (125)	% (/uL)	AST	1167	IU/L	IgE	3966	mg/dl
Mono	7 (875)	% (/uL)	ALT	1178	Iu/L	C3	50.1	mg/dl
Lymph	18 (2250)	% (/uL)	LDH	670	IU/L	C4	11.8	mg/dl
			ALP	387	IU/L			
RBC	484 x 10^4	/uL	γ GTP	141	IU/L	TSH	0.87	ng/dl
Hb	13.9	/dL	ChE	95	IU/L	Free- T3	1.7	μg/dl
Hct	42.4	/uL	BUN	12.8	mg/dL	Free-T4	1.1	μg/dl
Plt	7.3 x 10^4	/uL	Cr	0..95	mg/dL			
			Na	135	mEq/L	AMA	(-)	
PT%	20.0	%	K	4.2	mEq/L	LAC	(-)	
PT-INR	2.66		Cl	98	mEq/L			
D-dimer	11.0	ng/ml				HBs-Ab	(-)	
			CEA	3.0	ng/ml	HBc-Ab	(-)	
CRP	5.56	mg/dl	AFP	2	ng/ml	HCV-Ab	(-)	
Glu	94	mg/dl	PIVKA-II	34	mAU/ml			

Table 4

The summary of previously reported cases of Budd-Chiari syndrome associated with hypereosinophilic syndrome

No.	Year	Authors	Age, Sex	Gene mutation	Treatment of HES	Treatment of BCS	Outcome
1	1985	Elouaerblanc L et al [7]	61, F	undetected	steroid hydroxyurea	diuretics mesocaval-anastomosis	dead
2	1987	Walker M et al [8]	30, M	undescribed	undescribed	undescribed	improvement
3	1993	Vargas CA et al [9]	37, M	none	steroid	anticoagulation diuretics	improvement
4	1996	Zylbergerg H et al [10]	50, F	5q deletion	undescribed	anticoagulation	dead
5	2006	Inoue et al [11]	27, M	FIP1L1 PDGFR A	steroid	Interventional dilation	improvement
6	2011	Lin HK et al [12]	10, M	undescribed	steroid montelukast	percutaneous transhepatic angioplasty	improvement
7	2011	Mishchenko E et al [13]	42, F	JAK2 V617F	none	none	dead before treatment
8	2013	Dasari S et al [14]	27, M	JAK2 V617F	steroid	undescribed	undescribed
9	2018	Our case	54, M	none	steroid	anticoagulation→liver transplantation	improvement

Figure 1: The imaging studies of enhanced computed tomography (a) and ultrasound (b), angiography (c).

All examination could not visualize hepatic veins and hepatic venous flow.

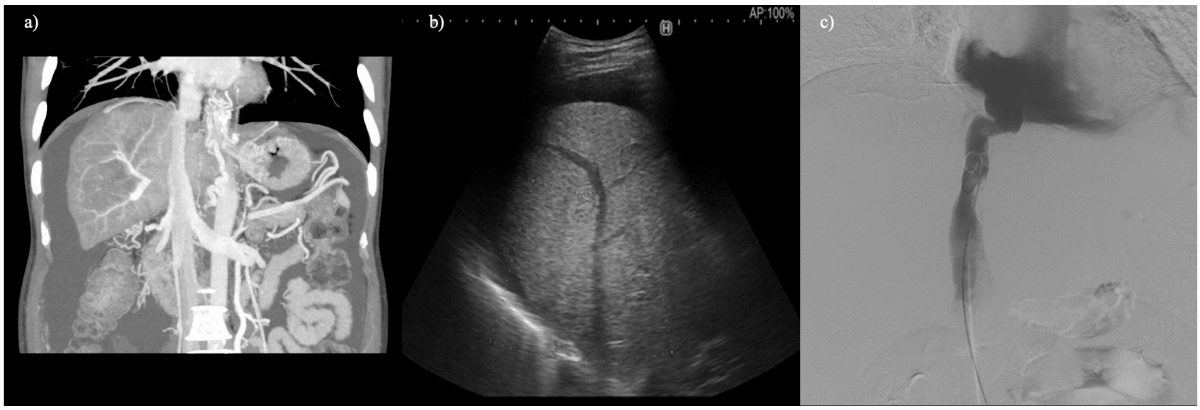

Figure 2: The clinical course.

Abbreviation: MP: methylprednisolone, PSL: prednisolone, TAC: tacrolimus

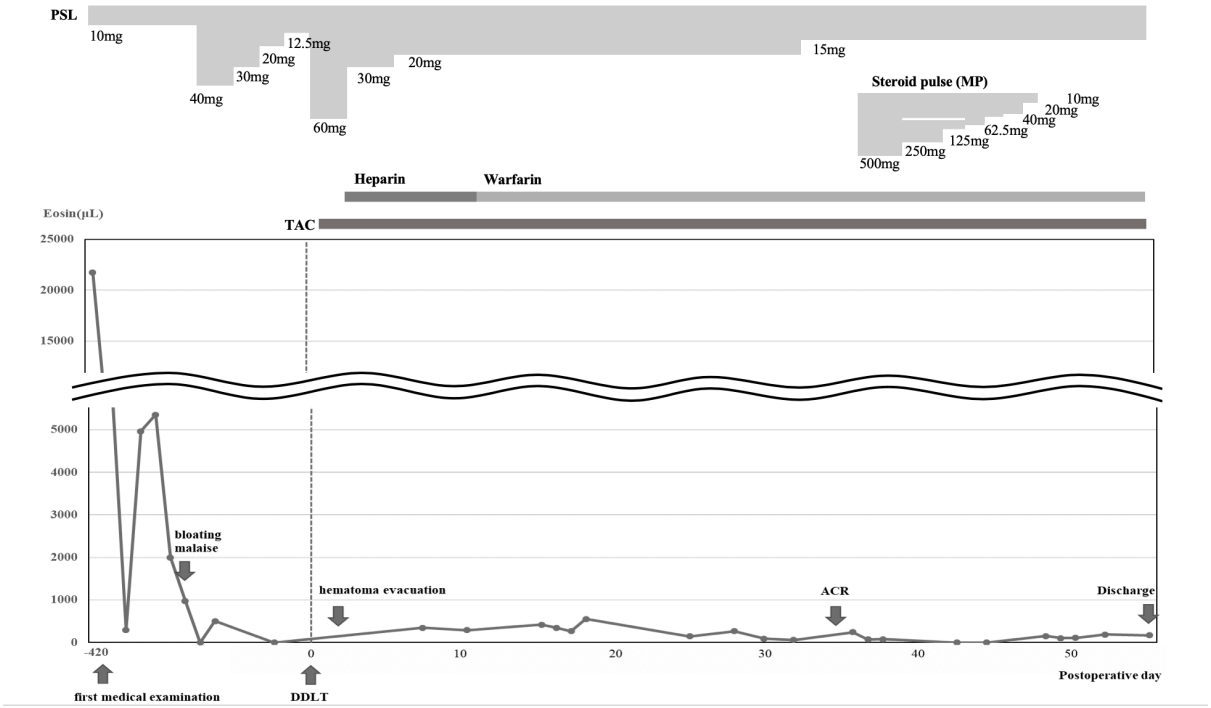

Figure 3: Macroscopic findings of explanted liver (a, b) and additional resected tissue around the hepatic veins (c).

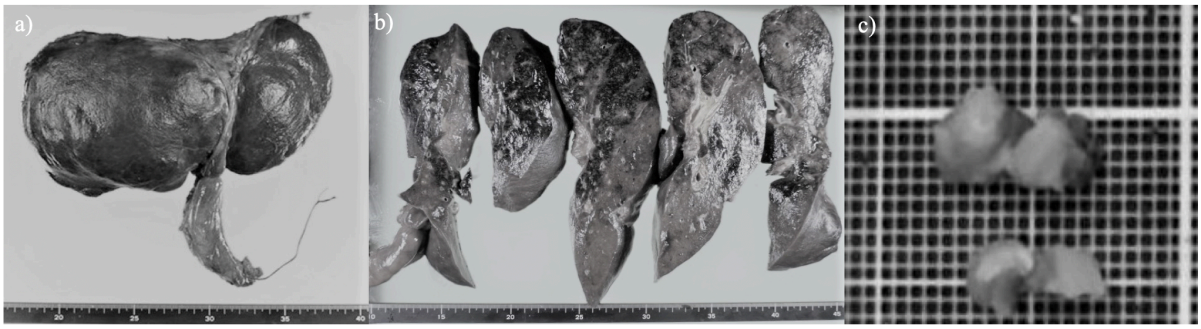

Figure 4: Histological findings of hepatic parenchyma (a, b) and hepatic veins (c, d).

a) H&E, x20 b) H&E, x20 c) H&E, x10 d) H&E, x100