INTERNAL MEDICINE

Successful Treatment of Ascites using a Denver® Peritoneovenous Shunt in a Patient with Paroxysmal Nocturnal Hemoglobinuria and Budd-Chiari syndrome

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Abstract

A 56-year-old man was diagnosed with aplastic anemia and paroxysmal nocturnal hemoglobinuria at 43 years of age and treatment with cyclosporin A was started. Liver cirrhosis, ascites, and thrombus in the hepatic veins were found at 56 years of age and Budd-Chiari syndrome (BCS) was diagnosed according to angiography findings. He was treated with diuretics and paracentesis was performed several times, but with limited efficacy. A Denver® peritoneovenous shunt (PVS) was inserted into the right jugular vein; his ascites and renal function improved immediately and his general condition has remained good for 12 months since starting the above treatment regimen. A PVS is a treatment option for ascites due to BCS.

Key words: Denver peritoneovenous shunt (PVS), Budd-Chiari syndrome (BCS), paroxysmal nocturnal hemoglobinuria (PNH)

Introduction

A case of aplastic anemia-paroxysmal nocturnal hemoglobinuria (AA-PNH) syndrome was initially reported as AA presenting with symptoms characteristic of PNH during the course of the disease (1-3). PNH is a rare acquired disorder of pluripotent hematopoietic stem cells that is characterized by intravascular hemolysis and venous thrombosis (4, 5). It is caused by a somatic mutation in the X-linked phosphatidylinositol glycan class A (PIG-A) gene, which is required for the synthesis of the glycosyl phosphatidylinositol (GPI) anchor. The mutation results in the absence of key complement regulatory proteins CD55 and CD59 (6-9). On erythrocytes, CD55 and CD59 deficiency leads to intravascular hemolysis upon complement activation. Intravascular

complement-mediated lysis results in anemia, hemoglobinuria, and venous thrombosis (4). Thrombotic events occur in 40% of PNH patients and hepatic vein thrombosis (Budd-Chiari syndrome; BCS) is the most frequent manifestation (40.7%) (10-12).

Thrombosis in a hepatic vein results in abdominal pain, hepatomegaly, and ascites, which are the characteristic findings in BCS (11, 13). The management of ascites involves treating thrombosis and thrombolysis (14-16). Percutaneous hepatic vein balloon angioplasty (17, 18) should be considered in early thrombosis. Anticoagulants are selected for long-term management (5, 19). Patients with thrombosis have a high risk of recurrence and anticoagulant treatment is necessary, although the duration of treatment is controversial because these patients also have a high risk of bleeding (5).

The accumulation of ascites is a common complication in

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BCS and medically intractable ascites can be treated with a peritoneovenous shunt (PVS) (18, 20), surgical portosystemic shunt (13, 21), transjugular intrahepatic portosystemic shunt (TIPS) (22-24), liver transplantation (13, 21), or paracentesis (20). Since Leveen et al. first reported the treatment of refractory ascites using a PVS (25), several modifications have been made. The Denver® PVS transfers fluid from the peritoneal space to the circulatory system and can be used to treat ascites (20).

We herein report the successful treatment of ascites using a Denver® PVS in a patient with PNH and BCS.

Case Report

A 56-year-old man was diagnosed with AA at 34 years of age and treated with cyclosporin A. He developed PNH at 43 years of age and was thought to have AA-PNH syndrome. At 56 years of age, his abdomen became distended and his weight increased from 66 to 72 kg in 2 weeks. He was admitted to our hospital to evaluate the weight increase (Fig. 1a). Biochemical data showed liver dysfunction and pancytopenia (Table 1). Computed tomography (CT) revealed liver cirrhosis, ascites, and thrombus formation in the left hepatic vein (LHV) and hepatic inferior vena cava with stenosis (Fig. 1b and c). The cause of thrombosis was thought to be AA-PNH. No other risk factors for BCS were found, such as JAK-V617F mutations (26) (Table 1).

Angiography showed stenosis of the hepatic inferior vena cava and hepatic veins due to thrombosis, with collateral formation (Fig. 1d and e). According to these findings, the patient was diagnosed with BCS. The right and middle hepatic veins were obstructed by thromboses. The thrombosis in the inferior vena cava was extremely large. Urokinase injection and balloon dilation of the LHV were performed several times. Heparin was administered for 2 weeks and then switched to warfarin at day 40. Although there was no change in the thrombosis, his weight and the ascites decreased and he was discharged on day 97.

He was re-admitted to our hospital for variceal bleeding on day 165 and endoscopic variceal ligation (EVL) was performed (Fig. 2a). After EVL, the ascites increased and was not controllable with diuretics. The increased ascites led to compartment syndrome and an altered renal function. In addition to paracentesis, cell-free and concentrated ascites reinfusion therapy (CART) was performed on days 200, 218, and 234. CART therapy was temporarily effective, however, the ascites re-accumulated rapidly a few days after drainage. The ascites was transudative, caused by cirrhosis and there was no evidence of infection. Because the right and middle hepatic veins and the hepatic inferior vena cava were obstructed by thrombosis, TIPS would have been ineffective. Therefore, we considered inserting a Denver® PVS. His heart function was normal according to echocardiography and he could tolerate the intravenous return of ascites. The day before the procedure (day 248), he weighed 67.8 kg and 3 L of ascites were drained to reduce the returned-volume of

ascites. On day 249, a percutaneous Denver® PVS was inserted by a surgeon from the right upper quadrant of the abdomen, subcutaneously through the thorax, and placed via the right internal jugular vein (Fig. 2b). During PVS insertion, warfarin was replaced by heparin. After the procedure was completed, warfarin was re-started. The urine flow increased to 4 L/day soon after transferring the ascites intravascularly. His weight decreased from 65.4 to 63.1 kg the next day. His renal function improved and the use of diuretics could be reduced (Table 1). His weight did not increase after inserting the PVS and he was discharged on day 259. His weight had decreased to 50 kg 1 month after discharge and his distended abdomen was obviously improved with reduced ascites (Fig. 2c). Although his weight had increased slightly 4 months after shunt insertion because his appetite had improved, the ascites was controlled according to abdominal and pelvic CT 4 months after discharge (Fig. 2d and e). While the thrombosis remained, it was found to have slightly diminished in size. His general condition was good, his quality of life had improved and he could finally return to work. Six months after inserting the Denver® PVS, the renal and liver function tests improved markedly (serum creatinine, 0.69 mg/dL; estimated glomerular filtration rate (eGFR), 92.7 mL/min/1.73 m^2; total bilirubin (T-BIL), 2.0 mg/dL; aspartate aminotransferase (AST), 21 U/L; and alanine aminotransferase (ALT), 15 U/L). Although his weight had increased, an estimation of the body components using an impedance assay showed that this was because his muscle mass had increased (Table 2). His esophageal varices became slightly enlarged at 10 months after PVS insertion.

Discussion

Our patient with AA-PNH syndrome who developed BCS and ascites was successfully treated using a Denver® PVS. Prior to treatment, urokinase injection, percutaneous transluminal balloon angioplasty (PTA) of the LHV, fibrinolytic therapy, and anticoagulation all failed to resolve thrombosis caused by AA-PNH. The PVS dramatically improved the patient's quality of life and his general condition was good at the 12-month follow-up.

Thrombosis results in a high morbidity and mortality. Overall, 40-67% of PNH patients will die of thrombotic complications and an initial thrombotic event increases the relative risk of death by 5- to 10-fold (27). Differences have been reported in the incidence of thrombosis in PNH (28). Thrombosis was observed at the diagnosis/follow-up in 19.3/ 31.8% of Western patients versus only 6.2/4.3% of Japanese patients (28). Significantly more Western patients died from thrombosis. Retrospective studies have suggested that the risk of thrombosis is correlated with the size of the PNH granulocyte clone (29, 30). A lower risk was reported in Chinese and Japanese patients, which is likely explained by a significantly lower PNH granulocyte size in these patients compared with Western patients (28). A survival analysis re-
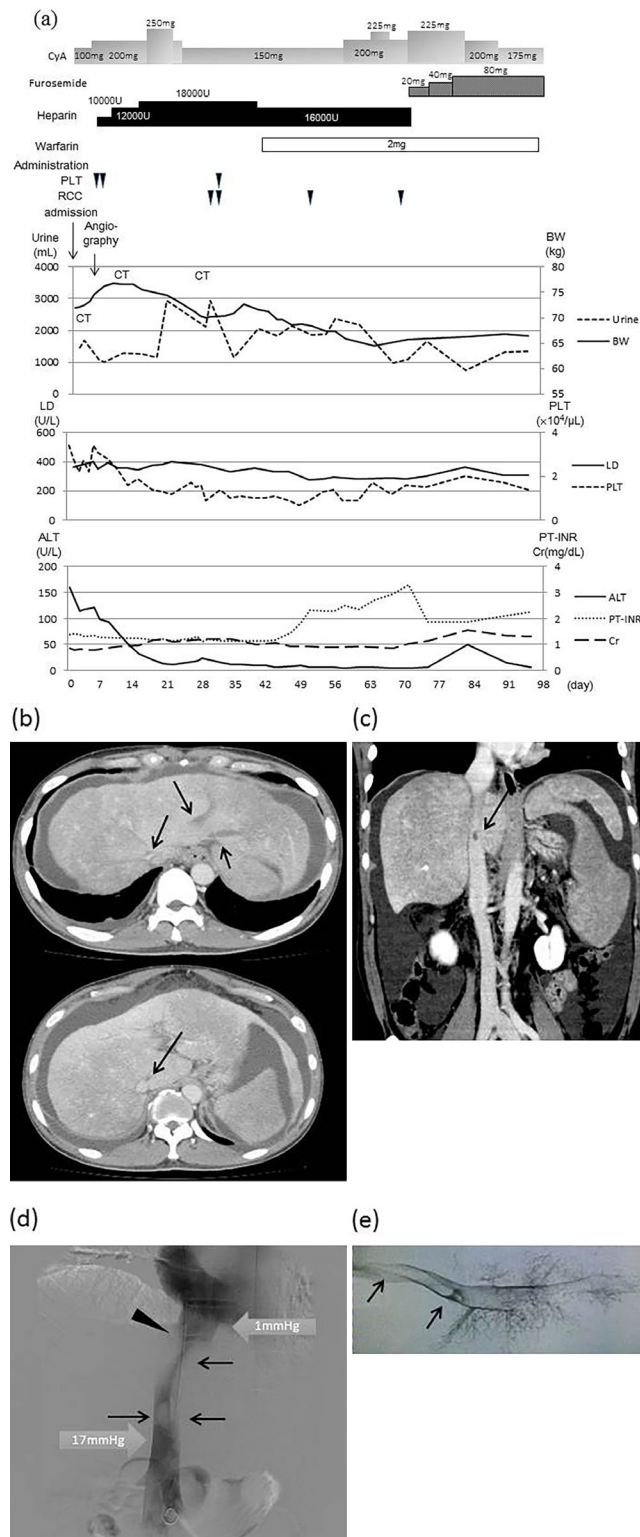
Figure 1. (a) Clinical course during the first admission. (b, c) Abdominal computed tomography (CT) on admission. (b) A transverse CT view through the middle abdomen shows liver cirrhosis, enlargement of the caudate lobe of the liver, and ascites (arrows: thrombi). (c) A coronal view of the middle abdomen shows thrombosis in the left hepatic vein (LHV) and stenotic inferior vena cava (IVC) with a thrombus. (d, e) Angiography of the abdominal veins. (d) The IVC was stenotic; the pressure in the IVC was 17 mmHg, and that in the right atrium was 1 mmHg (arrows: thrombi, triangle: IVC stenosis). (e) The LHV was obstructed with spider-like collateral formation and thrombosis; Budd-Chiari syndrome was diagnosed (arrows: thrombus). CyA: cyclosporin A, ALB: albumin, PLT: platelets, RCC: red cell concentrates stored in mannitol-adenine-phosphate solution, BW: body weight

Table 1. The Patient's Biochemical Data.

	On 1st admission	Day 178	After PVS insertion	Six months after PVS insertion
WBC (/μL)	4,960	4,870	2,550	2,120
RBC (×10^4/μL)	375	351	266	302
Hb (g/dL)	10.2	10.2	8.0	9.0
Ht (%)	30.7	30.1	24.9	27.7
PLT (×10^4/μL)	3.4	2.3	2.5	3.7
Ret (%)	2.6			2.5
TP (g/dL)	6.5	6.5	7.2	6.9
ALB (g/dL)	3.7	3.2	3.3	3.4
T-BIL (mg/dL)	2.3	5.2	2.0	1.9
D-BIL (mg/dL)	0.5	3.0	0.5	0.3
AST (U/L)	160	171	21	24
ALT (U/L)	160	114	15	12
LD (U/L)	452	487	340	294
ALP (U/L)	461	351	547	398
γ-GTP (U/L)	53	55	101	110
CRP (mg/dL)	0.76	3.62	3.40	0.30
Na (mEq/L)	141	132	140	143
K (mEq/L)	4.4	4.8	4.2	3.6
Cl (mEq/L)	105	98	106	108
BUN (mEq/L)	14.9	62.9	17.2	14.4
Cr (mg/dL)	0.92	3.73	0.69	0.81
eGFR (mL/min/1.73m^2)		14.7	92.7	77.8
TC (mg/dL)	125			
TG (mg/dL)	92			
FBS (mg/dL)	108			154
Hb$_{A1C}$ (%)	5.7			
PT (%)	51	42.1	34.2	21.9
PT-INR	1.39	1.61	1.82	2.51
APTT (sec)	39.2			
AT-III (%)	85			
Fibrinogen (mg/dL)	174			341
FDP (μg/mL)	15.7			4.5
D-dimer (μg/mL)	7.9			1.4
IgG (mg/dL)	1,168			
IgA (mg/dL)	244			
IgM (mg/dL)	94			
RF	(-)			
ANA	<20			
AMA M2	<1.5			
HBsAg	(-)			
Anti-HBc	(-)			
Anti-HCV	(-)			
Protein C activity (%) (64–146%)	45			
Protein S activity (%) (60–150%)	83			
Lupus anticoagulant	1.2			
Anti-CL-IgG Ab (U/mL)	≤8			
Jak2 mutation	(-)			
CyA (ng/mL)	116	180		

WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, Ht: hematocrit, PLT: platelets, Ret: reticulocytes, ALB: albumin, T-BIL: total bilirubin, D-BIL: direct bilirubin, LD: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyl transpeptidase, CRP: C-reactive protein, Na: sodium, K: potassium, Cl: chloride, BUN: blood urea nitrogen, Cr: creatinine, eGFR: estimated glomerular filtration rate, TC: total cholesterol, TG: triglycerides, FBS: fasting glucose, HbA1c: hemoglobin A1c, NGSP: national glycohemoglobin standardization program, PT: prothrombin time, INR: international normalized ratio, APTT: activated partial thromboplastin time, FDP: fibrinogen degradation product, RF: rheumatoid factor, ANA: antinuclear antibody, AMA: anti-mitochondrial antibody, Anti-CL-IgG Ab: anti-cardiolipin antibodies, JAK2: Janus kinase 2, CyA: cyclosporin A

vealed a similar death rate, however, Japanese patients had a longer mean survival time (32.1 vs. 19.4 years) (28).

A poor survival was associated with an age over 50 years,

severe leukopenia/neutropenia at diagnosis, and a severe complicating infection, in addition to complicating thrombosis at the diagnosis or follow-up in Western patients and renal failure in Japanese patients (28). Our case manifested predominantly as thrombosis in PNH. While this is rare in Japan, no other thrombosis risk factors, including the JAK2 mutation, were observed.

In the treatment of thrombosis, in addition to anti-thymocyte globulin plus cyclosporin (31, 32) and primary prophylaxis with vitamin K antagonists, such as warfarin (5, 19), the usefulness of eculizumab, a monoclonal antibody against complement factor C5, has been reported (33, 34). These agents effectively reduce intravascular hemolysis and thrombotic risk and have dramatically improved the prognosis of PNH (27). In our patient, fibrinolysis and anticoagulation therapy failed to resolve the thrombus. We suspected that the thrombus was mature and we could not increase the dosages of these agents because of the high risk of bleeding. Moreover, variceal bleeding altered the hemostatic system. Eculizumab was the next option, and we needed to consider its indications carefully.

The accumulation of ascites is the most worrisome complication of BCS and medically intractable ascites was treated with a shunt and drainage. Ascites control is achieved sooner after PVS insertion than after TIPS (73% vs. 46% after 1 month), although TIPS is favored for long-term efficacy (85% vs. 40% at 3 years) (23). PVS and paracentesis are reported to be equally effective at relieving refractory ascites (20). Liver transplantation has been performed to treat liver cirrhosis; however, the prognosis is poor, and thrombosis can recur (35-37). In our patient, thrombolysis, percutaneous hepatic vein balloon angioplasty, and warfarin treatment was partially effective, but not sufficient. We performed paracentesis several times, but its effect was temporary. Finally, the ascites was treated successfully for a longer period using a Denver® PVS.

Reported complications after Denver® shunt insertion include variceal bleeding, heart failure, shunt obstruction, disseminated intravascular coagulation (DIC), and pulmonary edema (38). In one study, DIC occurred in 37% of patients and was fatal in 78% (39). To reduce the risk of DIC, ascites should be drained prior to PVS insertion, which will reduce the intravenously returned volume (39). Minimizing the returned volume of ascites may also contribute to reducing the risk of heart failure and pulmonary edema (38). To prevent sepsis-induced DIC, ascites-induced infection should be ruled-out. In addition, heparin treatment will inhibit thrombus formation, bleeding, and the development of DIC. Although we could not control the speed at which the ascites returned, no severe complications of ascites were observed in our patient.

Variceal rupture was observed during the second hospitalization. A slight enlargement of the varices was seen 10 months after the insertion. As the PVS procedure is not a radical treatment of cirrhosis, the patient's remaining liver function was preserved after insertion and was not further
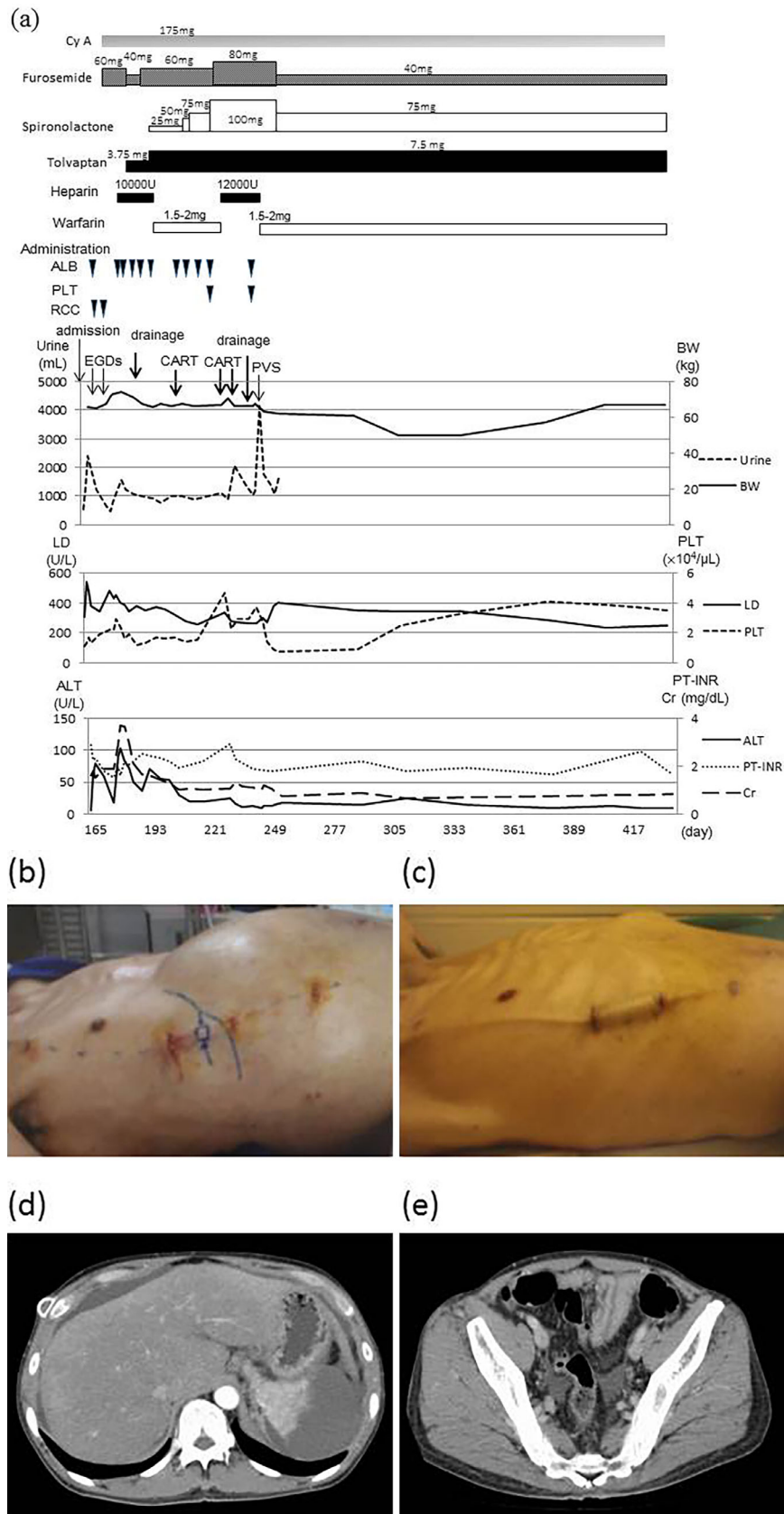
Figure 2.   **(a) Clinical course of the second admission. The abdomen (b) before and (c) 1 month after peritoneovenous shunt (PVS) insertion. (d, e) Abdominal and pelvic CT 4 months after discharge. Some ascites remained 1 month after PVS insertion; however, his distended abdomen was obviously improved. CyA: cyclosporin A, ALB: albumin, PLT: platelets, RCC: red cell concentrates stored in mannitol-adenine-phosphate solution, CT: computed tomography, BW: body weight**

Table 2. Body Composition Estimated by a Bioelectrical Impedance Analysis.

	Day 281	Day 439
Body weight (kg)	50.7	71.4
Skeletal muscle mass (kg)	22.8	32.3
Body fat mass (kg)	7.9	11.9

exhausted thereafter. Thus, PVS-treated patients are able to eat well, resulting in a better nutritional status. Following insertion, our patient's anticoagulant therapy was switched from warfarin to heparin; warfarin was re-started after the procedure. Warfarin administration was responsible for the decrease in the PT%; however, there was no reduction in his liver function.

Major prognostic factors for BCS are the prothrombin time, serum bilirubin level, creatinine, and presence of hepatic encephalopathy and ascites (18, 40). Control of ascites might be important for improving the prognosis. In our institution, five cases of BCS have been seen in the last 15 years, including the present case. The cause of BCS was unknown in the other cases. One case was treated with PTA and remained alive for 14 years. In three cases, PTA and thrombolysis were performed; however, two of these cases needed liver transplantation. In our patient, liver transplantation was contraindicated due to the complication of PNH, the future medical treatment of which is currently under consideration. In the interim, the Denver® PVS has been a useful treatment.

In conclusion, ascites control is important to improve the patient's quality of life and the prognosis of BCS. Although an improvement in the prognosis following PVS insertion remains to be confirmed formally, prior to treatment our patient was dying, whereas afterwards his nutrition improved and he was able to return to work. The Denver® PVS is one treatment option if paracentesis is effective, but is required multiple times for intractable ascites.

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

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