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Case Report

Reinfusion of Malignant Ascites through an Extracorporeal Peritoneal Venous Shunt to Avoid Complications and Assess the Safety of a Denver Shunt: A Case Report

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Keywords

Peritoneal venous shunt · Cell-free and concentrated ascites reinfusion therapy · Extracorporeal circulation of ascites · Gastric cancer · Denver shunt

Abstract

Introduction: Malignant ascites due to peritoneal metastasis of gastric cancer is challenging to manage, especially in frail and elderly patients. Traditional treatments like diuretics and paracentesis offer limited relief and can lead to complications such as malnutrition and dehydration. The Denver shunt, a type of peritoneal venous shunt (PVS), can alleviate symptoms but carries risks of severe complications like acute heart failure and disseminated intravascular coagulation (DIC). Assessing patient tolerance before Denver shunt insertion is crucial to prevent life-threatening events. ***Case Presentation:*** An 82-year-old woman with advanced gastric cancer developed refractory malignant ascites unresponsive to diuretics and cell-free and concentrated ascites reinfusion therapy (CART). Given her age and frailty, along with the small amount of blood in the ascites, there were concerns about the risks associated with a Denver shunt. An extracorporeal PVS was employed to reinfuse ascites at a controlled rate using an infusion pump. The infusion started at 40 mL/h and was carefully monitored. When the patient experienced paroxysmal supraventricular tachycardia at 60 mL/h, the rate was reduced, and β-blocker therapy was initiated. No signs of heart failure, infusion reactions, or DIC were observed during the 8-day extracorporeal reinfusion. After confirming stable laboratory tests including D-dimer levels which elevated slightly on day 3 and decreased on day 7 without intervention, a Denver shunt was safely inserted without severe complications. Thereafter,

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patient's ascites was effectively managed, not deteriorating her quality of life, until her passing away 2 months later. ***Conclusion:*** This case suggests that extracorporeal PVS, in which controlled reinfusion of ascites for several days can prevent acute complication and monitor potential adverse events, can be a valuable prior treatment before Denver shunt insertion in patients with malignant ascites, especially for frail and elderly patients.

Introduction

Gastric cancer is common and is the third leading cause of cancer-related deaths in Japan [1]. The most common symptoms at the time of gastric diagnosis were indigestion (dyspepsia), anorexia or early satiety, weight loss, and abdominal pain. In unresectable and recurrent gastric cancer, the peritoneum is a common metastatic site, which causes massive ascites, hydronephrosis, and bowel obstruction, and diminishes the quality of life [2].

Various factors contribute to the development of ascites, including increased peritoneal capillary permeability due to disseminated tumor nodules, decreased absorptive capacity due to extensive peritoneal adhesions, impaired venous return, obstruction of the lymphatic system due to cancer cell infiltration, and low intravascular water retention due to hypoproteinemia associated with malnutrition. As there is no specific or effective treatment for these issues, diuretics such as furosemide, spironolactone, and tolvaptan are commonly used, and the drainage of ascites by peritoneal puncture plays a central role in relieving the symptoms caused by massive ascites [3]. However, it is difficult to control ascites, and repeated drainage often causes exhaustion, which is associated with malnutrition and intravascular dehydration.

The Denver shunt is a type of peritoneal venous shunt (PVS) that is often used to relieve symptoms of refractory ascites caused by peritoneal dissemination of cancer or portal hypertension, such as liver cirrhosis. The rapid influx of ascites into the blood vessels causes heart failure and pulmonary edema in 3–16% of patients, and disseminated intravascular coagulation (DIC) in 27–40% of patients [4–6]. These complications can be life threatening. In a recent report of 31 cases of cancerous peritonitis in which a Denver shunt was placed to control refractory ascites, DIC followed by death within 20 days of surgery was observed in 3 cases (9.7%), and heart failure was observed in 2 cases (6.0%), of which 1 died on day 19 [7]. Since there are several severe complications, patients must be carefully evaluated for indications for a Denver shunt. Here, we report a case in which we used an extracorporeal PVS to assess the indications for a Denver shunt, which was later inserted without complications.

Case Presentation

An 82-year-old woman with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 2 was referred to our hospital for investigating the cause of iron deficiency anemia. Upper gastrointestinal endoscopy revealed a type 3 gastric tumor in the antrum, extending to approximately half the circumference of the lower gastric body. Pathology revealed a moderately differentiated adenocarcinoma. Computed tomography (CT) revealed lymph node metastasis, which was diagnosed as clinical stage IIIC (cT4aN3M0) gastric cancer (TNM classification, 8th edition). As the cytology of the ascites showed adenocarcinoma

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immediately after starting surgery, palliative laparoscopic distal gastrectomy was performed in February.

After surgery, the patient was treated with S-1 combination therapy (80 mg/m^2) on days 1–14. In March, S-1 plus oxaliplatin was initiated at 100 mg/m^2 on day 1 every 3 weeks, without nivolumab due to patient's concerns regarding adverse immune-related reactions. After 15 courses, an abdominal CT scan revealed disease progression with increased pleural fluid and ascites. Chemotherapy was changed to a combination of albumin-bound paclitaxel at 100 mg/m^2 and ramucirumab at 8 mg/kg on days 1 and 15, which was repeated every 4 weeks. When subconjunctival hemorrhage and severe edema were developed by ramucirumab and paclitaxel, the second-line chemotherapy was discontinued. Because there were limited available active drugs, the third-line chemotherapy with nivolumab at 240 mg/body every 2 weeks was started after obtaining the patient's consent. After four cycles, the patient experienced abdominal distention, and a CT scan revealed ovarian metastasis and increased ascites. The treatment was changed to oral trifluridine/tipiracil at 80 mg/day on days 1–5 and 8–12, every 4 weeks in May, and diuretics, furosemide, and spironolactone were prescribed. Thereafter, the ascites increased, and cell-free and concentrated ascites reinfusion therapy (CART) was performed every 2 weeks to relieve abdominal distension. Her oral intake and daily activity were improved by CART, but were deteriorated soon as the ascites increased rapidly despite slight shrinkage of the ovarian metastasis (stable disease according to the Response Evaluation Criteria in Solid Tumors [RECIST]), and weekly CART was required to control her ascites until late October.

For the continuous reduction of abdominal distention, we discussed about the construction of a Denver shunt. Since the patient was old and frail with signs of blood in her ascites, insertion of the conventional Denver shunt was considered dangerous for fear of the associated risk of severe complications such as acute heart failure, DIC, and thrombosis. Consequently, extracorporeal PVS using an infusion pump was proposed, considering that the infusion speed could be controlled by a pump for preventing acute heart failure and infusion could be stopped immediately after DIC or thrombosis would occur under the close monitoring. After discussing the risk-benefit balance in the medical safety committee which was composed of doctors, pharmacists and nurses, this procedure was approved. A schematic diagram of the extracorporeal PVS using an infusion pump is shown in the online supplementary Figure (for all online suppl. material, see https://doi.org/10.1159/000543892).

The patient provided informed consent for extracorporeal reinfusion of ascites in October, when physical examination showed abdominal distention but normal vital signs, and laboratory tests revealed no renal, liver, or other organ dysfunction (Table 1). Abdominal CT upon admission showed massive ascites and ovarian metastasis (Fig. 1a).

On day 1, an echo-guided abdominal puncture was performed in the right lower abdomen and a central venous (CV) catheter was placed and connected to a sterile (phlebotomy) bag that served as a reservoir for ascites, which was continuously recycled to the body through the CV port, with the infusion rate controlled by an infusion pump at 40 mL/h. The ascites was classified as exudative associated with minute extravasation of blood (not active bleeding) because they contained traces of blood (blood cell count of 2.8×10^4/μL) and showed high LDH and protein levels (Table 2). No signs suggestive of heart failure such as dyspnea, hypotension, or tachycardia were noted. The perfusion rate was increased to 60 mL/h on day 2, but when paroxysmal supraventricular tachycardia occurred on day 3, the infusion rate was immediately decreased to 20 mL/h and a bisoprolol, β-adrenergic blocking drug, was prescribed. Thereafter, no arrhythmia was observed, and the perfusion rate returned to 40 mL/h on day 5. No fever or shivering chills (indicative of an infusion reaction) were observed during perfusion. Anticoagulants were not started for fear of intra-abdominal bleeding. While the D-dimer level increased to 39.8 mg/dL on day 3, it gradually decreased without medication.

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Table 1. Laboratory data prior to extracorporeal PVS

Blood cell count	
WBC, /μL	6,440
Neu, %	80.0
RBC, /μL	387 × 10^4
Hb, g/dL	13.7
Hct, %	40.3
MCV, fL	104.1
MCH, pg	35.4
Coagulation	
PT-INR	1.01
APTT, s	22.9
Fib, mg/dL	380
D-dimer, μg/mL	3.6
Biochemical test	
TP, g/dL	6.1
Alb, g/dL	3.2
BUN, mg/dL	36.3
Cre, mg/dL	1.19
eGFR, mL/min/1.73m^2	34.0
AST, U/L	70
ALT, U/L	32
LDH, U/L	475
ALP, U/L	60
γ-GTP, IU/L	37
Amylase, U/L	120
UA, mg/dL	9.0
T-Bil, mg/dL	0.6
Na, mEq/L	138
K, mEq/L	3.1
Cl, mEq/L	93
Glucose, mg/dL	122
CRP, mg/dL	0.10

WBC, white blood cell; Neu, neutrophils; RBC, red blood cell; Hb, hemoglobin; Hct, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; PT-INR, prothrombin time international normalized ratio; APTT, activated partial thromboplastin time; Fib, fibrinogen; TP, total protein; Alb, albumin; BUN, blood urea nitrogen; Cre, creatinine; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine transferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; γ-GTP, γ-glutamyl transpeptidase; UA, uric acid; T-Bil, total bilirubin; Na, sodium; K, potassium; Cl, chloride; CRP, C-reactive protein.

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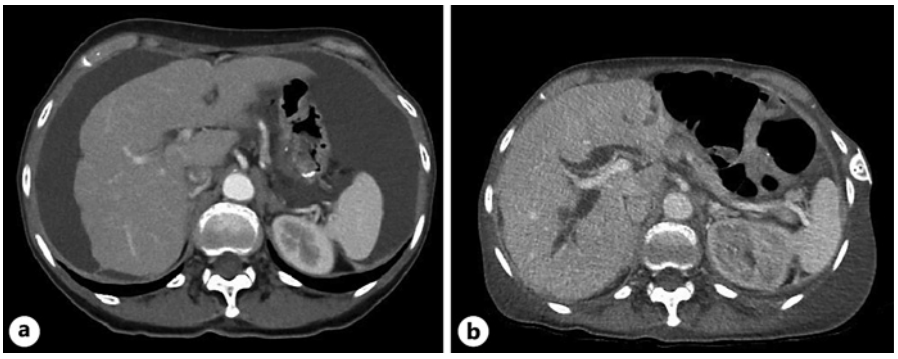

Fig. 1. Abdominal CT. **a** Before extracorporeal PVS. **b** 15 days after insertion of the Denver shunt.

Platelet counts decreased slightly, but remained within normal limits. The diagnostic criteria for DIC were not met (Fig. 2). Since no severe complications were observed over 8 days with the extracorporeal PVS, and abdominal distention was improved, the patient was transferred to the interventional radiology division of a specialty cancer hospital where a Denver shunt was successfully placed, resulting in the reduction of ascites on day 9 (Fig. 1b). Thereafter, no adverse events were experienced due to the Denver shunt, except edema in the left arm and thrombosis near the CV catheter in the left subclavian vein, which were quickly dispersed by anticoagulation therapy. The abdominal distention was ameliorated for 2 months until the patient died.

Discussion

The primary treatment for ascites due to peritoneal cancer metastasis consists of eliminating cancer cells in the abdominal cavity using antitumor treatments such as chemotherapy. A randomized study targeting gastric cancer patients with severe peritoneal metastasis showed that ascites decreased in 27.5% and 36.2% of patients during first-line fluorouracil-based chemotherapy with fluorouracil/L-leucovorin and in combination with paclitaxel, respectively [8]. In a retrospective study of this population, ascites decreased in 17% and 51% of patients following first-line chemotherapy with fluoropyrimidines alone and in combination with platinum, respectively [9]. However, while the proportion of patients with malignant ascites increases with disease progression, especially in the later clinical course of gastric cancer, and late-line chemotherapy is generally ineffective in controlling malignant ascites. In this case, although the size of the ovarian metastasis decreased slightly, the ascites was not controlled by fourth-line systemic chemotherapy, and additional treatment strategy was required to control the ascites and relieve the associated symptoms.

The conventional medical interventions for ascites include sodium restriction and diuretics. Diuretics tend to decrease the ascites volume with a higher serum ascites albumin gradient. However, in cancer patients, ascites caused by peritoneal metastasis is generally exudative, and the benefits of diuretics remain controversial [10]. In the present case, ascites could not be controlled with diuretics. Abdominal distention by refractory ascites is best managed by large-volume paracentesis [11]. However, repeated ascites drainage causes protein loss, which decreases the ability of the serum to retain water, leading to increased ascites in a vicious cycle that shortens the life expectancy [12].

CART, originally developed for hepatic ascites, filters ascitic fluid through special membranes to remove water, cells, and bacteria, while concentrating protein. Although

Table 2. Laboratory data of ascites prior to extracorporeal PVS

Blood cell count	
WBC, $\times 10^2$ μL	4.28
RBC, $\times 10^4$ μL	2.8
Biochemical test	
TP, g/dL	2.6
Alb, g/dL	1.6
LDH, U/L	323
Amylase, U/L	61
Lipase, U/L	22.0
Ferritin, ng/mL	151
Na, mEq/L	141
K, mEq/L	2.4
Cl, mEq/L	100
Glucose, mg/dL	78
Total cholesterol, mg/dL	50

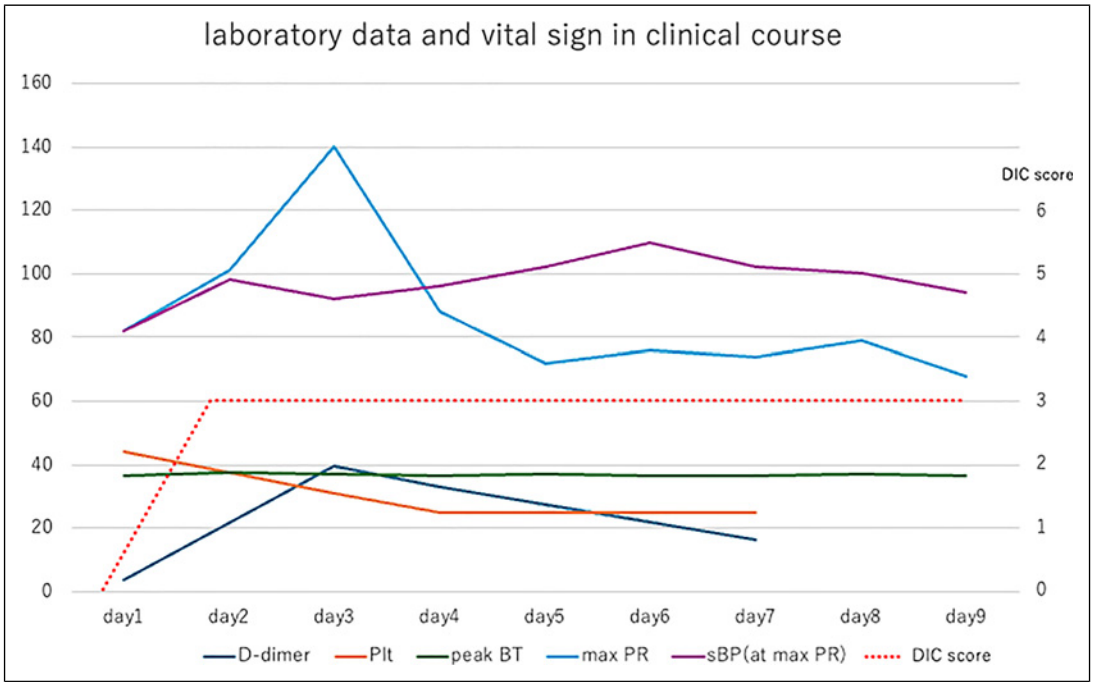

Fig. 2. Clinical course over 8 days of extracorporeal ascites circulation.

biweekly CART is covered by Japanese social insurance, ascites distention progressed in this case.

We considered that ascites could be controlled by a Denver shunt, which is equipped with a pump chamber and a nonreturn valve, allowing for the pumping of ascites by finger pressure and persistent perfusion of ascites [13]. Its success rate of symptom palliation was reported to be as high as 92.3% for chylous ascites [14], 80–88% for hepatic ascites [15], and 82.7–85.7% for cancerous ascites [16], although the prognosis has not improved [17]. However, a Denver

shunt causes some adverse events such as acute heart failure, infusion reaction, DIC, and thrombosis. Furthermore, bloody ascites is one of the contraindications for reinfusion of malignant ascites, and gastric cancer is known as high risk for deep vein thrombosis.

Before performing this procedure, this patient's prognosis was assumed to be about 1 month considering from 5 points in Palliative Performance Index, in which palliative performance scale of 30 was 2.5 points and severely reduced oral intake was 2.5, not associated with edema, dyspnea at rest, and delirium. It was afraid that ascites drainage repeated frequently should deteriorate patient's condition more rapidly. However, because her daily activity (performance status) and oral intake had been improved by CART, it was expected that controlling ascites could resolve these two problems leading to not only improvement of the patient's quality of life but also prolongation of patient's prognosis. In contrast to these expected benefits, adverse events such as acute heart failure and coagulopathy (thrombosis and DIC) caused by reinfusion of ascites were the risks. Although bloody ascites is one of the contraindications for reinfusion of malignant ascites, it was anticipated that minute blood cells and other substances contained in the ascites might cause DIC but less likely major thrombosis, and that DIC could be prevented or resolved by stopping the reinfusion and prompt management. Therefore, we monitored the patients intensively by asking the symptoms, checking the vital signs frequently, monitoring the electrocardiogram continuously, and repeating laboratory tests of coagulation factors during the first week. Furthermore, we decided that this procedure should be stopped if symptoms caused by thrombosis, acute heart failure, and DIC were observed. These risks and benefits were discussed by the medical safety committee in our hospital, and this procedure was allowed before starting this procedure.

With the Denver shunt, the rate of ascites perfusion is dependent on the pressure difference between the abdominal cavity and bloodstream. Large volumes of ascites generate high pressure, which may cause acute heart failure early in the conventional Denver shunt, with an incidence of 3% [16]. Our extracorporeal PVS was performed with the perfusion rate controlled using an infusion pump in the middle of the extracorporeal circuit. The patient experienced arrhythmia, a sign of heart failure, when the ascites was perfused at 60 mL/h; however, this was quickly resolved by reducing the reinfusion rate to 20–40 mL/h. After the reduction of the ascites volume by extracorporeal reinfusion, a Denver shunt was safely introduced, and the risk of acute heart failure was avoided. In a report of the 10 patients with malignant ascites not suited for conventional peritoneovenous shunts, for whom externalized peritoneovenous shunt was placed using a conventional a PVS kit (Denver-PAK; Denver Biomaterials, Inc., USA) without controlling the infusion speed by an infusion pump, three early death within 7 days occurred (renal failure due to preexisting hypovolemia in 2 patients, and one pulmonary edema in 1), and there were no severe adverse events in other 7 patients [18]. It is considered that pulmonary edema could be prevented if the infusion speed was controlled by a pump similar to our case. Additionally, it is important to pay attention to the organ function before the procedure. In this case series, the externalized peritoneovenous shunt could be exchanged to conventional Denver shunt sequentially, improving the subjective symptoms in 6 (60%) patients. It is suggested that well-controlled externalized peritoneovenous shunt may be useful pretreatment switching to the conventional Denver shunt for patients with adequate organ function.

The incidence of infusion reactions characterized by fever and chills after CART was reported to be 26.6% [19]. The removal of IL-6 using a β2-microglobulin adsorption column in vitro prevented this inflammatory response in one study [20], but in contrast, inflammatory cytokines IL-6, IL-8, and IL-10 in ascites have been reported to have no correlation with fever [21]. Thus, while the relationship between inflammatory cytokines and fever is controversial, a previous study of 228 procedures showed that the reinfusion rate (≥125 mL/h) and the rate

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of infusion of total protein in ascites (≥10.9 g/h) were correlated with the occurrence of adverse effects [22]. Although we did not measure inflammatory cytokines in the ascites of this case, it is likely that the slow extracorporeal circulation prevented an infusion reaction. Furthermore, if an infusion reaction had occurred, extracorporeal circulation could have stopped immediately.

DIC is a major concern in Denver shunts because it is reported to occur within week 1 in 5.3% of cases [16]. DIC may be initiated by thrombogenic factors such as tissue factors [23], but no clear cause has been identified [16], and methods for preventing DIC associated with the Denver shunt have not been well studied. In this case, as the ascitic fluid was pink, it likely contained blood-derived clotting factors. One study found that the risk of DIC was reduced by replacing the drained ascites with 5–6 L of saline to avoid the rapid infusion of potentially high concentrations of DIC-inducing substances into the ascites [24–26]. However, this replacement procedure has some drawbacks, such as abdominal bloating. In the present case, D-dimer was slightly elevated for 3 days, suggesting that the ascites contained some DIC-inducing substances. Thereafter, the D-dimer level gradually decreased, and the patient did not show signs of DIC during the 8 days of extracorporeal ascites reinfusion or after insertion of the Denver shunt. It is speculated that the slow rate of extracorporeal reinfusion could prevent DIC.

Furthermore, insertion of a Denver shunt requires an interventional radiologist and specialized medical equipment. Because the procedure requires only commonly available medical equipment – such as CV catheter, infusion bag, infusion pump, and bedside ultrasound device – we believe that extracorporeal circulation for malignant ascites can be performed even without special technique.

Conclusion

This case suggests the utility of extracorporeal circulation of malignant ascites for assessing safety and preventing complications associated with a Denver shunt. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material.

Acknowledgment

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Statement of Ethics

At the time of writing the case report, the patient had already passed away. Ethical consent for the publication of the case details was obtained from the patient's next of kin, who provided permission on behalf of the deceased. The patient's next of kin was fully informed of the nature of the case report and the intention to publish the findings. He agreed to the publication and provided written consent, acknowledging that the report would contribute to medical knowledge and understanding. In our institution, case reports do not require approval from the ethics committee (Research Ethics Committee, The Institute of Medical Science, The University of Tokyo) for publication. Therefore, institutional approval was not necessary for publishing the details of this case. Written informed consent was obtained from the patient's next of kin by the corresponding author. Details of the patient have been anonymized as much as possible.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

K.B., T.T., and N.B. contributed to the study design and manuscript preparation. All authors, including Y.M., Y.H., and H.I., reviewed the manuscript and approved its final content.

Data Availability Statement

The data supporting the findings of this study are available upon request from the corresponding author, K.B. Due to privacy and ethical considerations, some restrictions may apply to the data.

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