CASE REPORT

Steroid-Refractory Protein-Losing Enteropathy with Gastrointestinal Bleeding in a Patient with Fontan Circulation
A Case Report and Literature Review

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Summary
Protein-losing enteropathy (PLE) is one of the major complications after a Fontan operation. Some PLE patients suffer from concurrent gastrointestinal bleeding. An effective treatment regimen for such patients has not been established yet. Further, it remains unknown whether PLE and gastrointestinal bleeding coexist independently, or protein losing is associated with gastrointestinal bleeding. We report a 7-year-old steroid-refractory post-Fontan PLE case suggesting the latter pathogenesis together with a literature review.

Key words: Hypoalbuminemia, Anemia, Hypoplastic left heart syndrome, Total cavopulmonary connection, Steroid

Protein-losing enteropathy (PLE) is one of the major complications after a Fontan operation, and it occurs in about 5-15% of the cases. Despite recent advances, the prognosis remains poor. The mechanism of PLE remains largely unclear, but elevated central venous pressure (CVP), low cardiac output, inflammation, and immune or lymphatic system abnormality are known to be associated with the occurrence of PLE. Although some PLE patients can go into remission after a hemodynamic improvement or medical therapies such as systemic steroid administration, there are refractory PLE cases. An effective treatment regimen for such cases has not been established. More importantly, some PLE patients, although rare, exhibit concurrent gastrointestinal (GI) bleeding. Among these patients, it remains unknown whether PLE and GI bleeding coexist independently, or protein losing is associated with the GI bleeding. We report a steroid-refractory post-Fontan PLE case suggesting the latter.

Case Report
A 7-year-old boy with hypoplastic left heart syndrome (HLHS) after total cavopulmonary connection (TCPC) and tricuspid valve re-placement was admitted to our center for progressive anemia and hypoalbuminemia. His heart disease had been postnatally diagnosed as HLHS with mitral atresia, aortic atresia, moderate tricuspid insufficiency, and restrictive foramen ovale after full term delivery (38 weeks and 0 days, birth weight of 3068 g). His surgical and catheter intervention history is summarized in Table I. Cardiac catheterization performed when the patient was 4 years old (1 year after TCPC) revealed elevated CVP (21 mmHg), pulmonary capillary wedge pressure (PCWP, 17 mmHg), and right ventricular end-diastolic pressure (RVEDP, 14 mmHg) with maintained cardiac index (CI, 4.0 L/minute/m²), reduced pulmonary blood flow to systemic blood flow ratio (Qp/Qs, 0.73), and normal pulmonary vascular resistance (Rp, 1.2 unit*m²) indicating reduced right ventricular diastolic dysfunction as the main cause of his elevated Fontan pressure. The patient had received warfarin, aspirin, pulmonary vasodilators, and anti-heart failure therapies, as well as home oxygen therapy.

Before his admission at 7 years, the patient had been previously admitted for two days to undergo a detailed hormonal assessment to investigate his short stature. He suffered from diarrhea and abdominal pain a day later (day 0). Laboratory tests at the outpatient clinic on day 10 indicated mild hypoalbuminemia (serum total protein (TP, g/dL) 5.3, serum albumin (Alb, g/dL) 3.6, hemoglobin (Hb, g/dL) 13.4) (Figure 1). Although his diarrhea disappeared by day 12, he repeatedly showed loss of activity. On day 24, hypoalbuminemia and anemia progressed (TP 5.1, Alb 3.2, Hb 11.8) despite decreasing body weight. We tentatively diagnosed PLE after TCPC considering his clinical course and negative urinary protein, and initiated oral prednisolone (PSL, 0.5 mg/kg/day). However, the hy-
poalbuminemia and anemia further progressed (TP 4.7, Alb 2.5, Hb 10.6) on day 31, and we increased the PSL dosage up to 2.0 mg/kg/day. The patient was admitted to our center on day 38 because of apparent GI bleeding, hyponatremia (Na 123 mEq/L), and progressive hypoalbuminemia and anemia (TP 4.4, Alb 2.7, Hb 10.5).

At the time of admission, his body temperature was 37.2°C, systolic blood pressure was 80 mmHg, heart rate was 100 bpm, and respiratory rate was 20/minute. His percutaneous oxygen saturation (SpO₂) under oxygen administration of 1 L/minute by nasal cannula was 91%. Echocardiography showed unremarkable findings. Prothrombin time international ratio (PT-INR) values were within the target range after replacement by mechanical valve. No coagulation abnormalities other than an appropriate increase in the prothrombin time international ratio by warfarin were observed. After admission, the stool color gradually turned to black and red with stool human Hb level > 1000 μg/g, and serum albumin level showing a corresponding reduction (Figure 1). Medical therapies such as intravenous PSL and proton pump inhibitor therapy for a possible ulcer were ineffective even after low-dose aspirin and clopidogrel treatment was discontinued. We decreased the PSL dosage and eventually discontinued it. However, tarry stools persisted. Although stool cultures did not provide any pathogens, both Clostridium difficile (CD) antigen and toxin⁷ were detected on day 49. However, oral vancomycin over 10 days for possible CD infection (CDI) did not improve his PLE/ tarry stools.

Because fecal alpha1 antitrypsin clearance⁸ was as high as 90.6 mL/day on day 44, we definitively diagnosed his condition as PLE. Gastrointestinal scintigraphy using ⁹⁹mTc-labeled human serum albumin (day 44) showed protein losing and/or bleeding in the small intestine (Figure 2). A Meckel diverticulum was ruled out by scintigraphy on day 58. We performed red cell concentrate, albumin (indicated by arrows in Figure 1), and gamma globulin transfusion. Upper and lower gastrointestinal endoscopy on day 92 showed superficial gastritis, fragile duodenal membrane, and mild lymph duct dilation, but did not detect an ulcer or an active bleeding point. Fluid management to lower CVP, continuous heparin administration, reduced warfarin usage (PT-INR about 1.5), a low residue diet, and resting in bed over a period of several months stabilized the patient. As the GI bleeding improved, serum albumin levels increased (from 2.0 to 3.6 g/dL)(Figure 1). During the course of treatment, the serum albumin level decreased when GI bleeding increased, and the serum albumin level increased when GI bleeding improved with high reproducibility (Figure 1). Finally, both the GI bleeding and serum albumin level improved (TP 6.2, Alb 4.1, Hb 11.7), and he was discharged from our hospital on day 192.

**Table 1. Surgical and Catheter Intervention History**

| Age         | Intervention                                                                 |
|-------------|------------------------------------------------------------------------------|
| 1 day       | Balloon atrial septostomy                                                    |
| 9 days      | Bilateral pulmonary arterial banding & ductal stent implantation             |
| 5 months    | Norwood operation                                                            |
| 9 months    | Bidirectional Glenn operation & tricuspid valve replacement, left pulmonary   |
| 2 years 7 months | Tricuspid valve re-replacement                                             |
| 3 years 2 months | Coil embolization for aortopulmonary collateral arteries                   |
| 3 years 2 months | Extracardiac total cavopulmonary connection                                   |

**Figure 1.** Relationship between serum albumin level and stool human hemoglobin level reflecting the severity of bloody stool. The decrease in serum albumin level paralleled the extent of GI bleeding. Real line arrows show the albumin transfusion. Alb indicates albumin; and Hb, hemoglobin.

**Discussion**

In this case, a 7-year-old boy with Fontan circulation had elevated CVP, GI bleeding, and PLE. The reduction in serum albumin level paralleled the extent of GI bleeding with high reproducibility (Figure 1). In this case, sys-
The patient’s clinical course indicated that the PLE was strongly associated with GI bleeding. To our knowledge, only 6 cases of post-Fontan PLE complicated with concurrent GI bleeding have been reported (Table II).6,9-11 Importantly, steroid use was only mentioned in two cases, even though this is a key pharmacotherapeutic option for PLE.12 However, the patients in both of those cases responded insufficiently to budesonide therapy. Our case did not respond to PSL either. It can be postulated that steroids are not effective for combined PLE and GI bleeding in patients with Fontan circulation. This hypothesis needs to be verified by future studies.

This patient has tricuspid mechanical valve and Fontan circulation. He experienced prosthetic valve thrombosis requiring re-placement of the mechanical valve despite being under optimal warfarin therapy. Hence, anticoagulation needed to be maintained despite active GI bleeding which posed a clinical dilemma. Importantly, the severity of the GI bleeding (increase of human stool Hb) paralleled the worsening of PLE (decrease of serum albumin level) (Figure 1). Among case studies of Fontan circulation with both PLE and GI bleeding, to the best of our knowledge, only two reported video capsule endoscopic findings. One revealed congested edematous duodenum with macroscopic bleeding60 and the other revealed non-specific signs of duodenitis.61 The latter did not prove lymphangiectasia but indicated inflammation with an increased number of intraepithelial lymphocytes.61 The pathophysiologic mechanisms underlying GI bleeding in PLE are not completely understood.60 In a report of a case of non-Fontan PLE with GI bleeding, the authors histopathologically demonstrated blood-filled lymphatics and postulated the existence of latent lymphatic-venous connections that may open and allow the flow of blood into the lymphatic system under certain abnormal conditions.60 Seewoodhary, et al postulated that mechanistically, GI blood loss in PLE is due to the disruption of basement membrane integrity to such a degree that erythrocytes may translocate through gap junctions widened by exposure to proinflammatory cytokines.60 As the patient’s poor condition precluded us from performing video capsule endoscopy or biopsy, we were unable to evaluate the intestinal lesions directly responsible for the PLE and GI bleeding in our case. Given the scarce and inconsistent data, further accumulation of endoscopic and biopsy findings is definitely needed to deepen the understanding of the pathogenesis of combined PLE and GI bleeding.

During the course of treatment, CDI was detected in this case. Not checking for CDI during the early stages of treatment is a limitation of this study. This prevented us from judging the effect of CDI on the onset of PLE and GI bleeding. Since CDI can cause not only GI bleeding but also PLE,60 CDI should have been checked at the onset of PLE.

In conclusion, we report a subgroup of PLE with concurrent GI bleeding. In this subgroup of patients, there are no reports indicating the usefulness of systemic steroid administration (Table II). To develop an effective treatment strategy for these patients, multicenter registration of PLE in patients with Fontan circulation is definitely needed.

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Disclosure

Conflicts of interest: The authors have no conflicts of interest or funding to disclose associated with this manu-
### Table II. Case Reports of Protein-Losing Enteropathy with Gastrointestinal Bleeding in Patients with Fontan Circulation

| Basal heart disease (Ref. no.) | Prior valve surgery | Age at the onset of PLE | Sex | Effect of Steroid | Overall medical therapy | Surgical intervention for PLE | Outcome |
|--------------------------------|---------------------|-------------------------|-----|-------------------|-------------------------|----------------------------|---------|
| Unbalanced AVSD (Yasag)        |                     |                         |     | Not mentioned     | No detailed description | Recreation of fenestration, atrioventricular valve repair | Transient resolution and recurrence after surgical intervention. Cardiac transplantation. |
| Double inlet left ventricle (Yasa) |                     |                         |     | Not mentioned     | No detailed description | Fontan takedown | Improvement despite persistent hypoalbuminemia. Complete resolution |
| Tricuspid atresia (Yasag)       | -                   | 4                       | -   | Not mentioned     | Lowering ventricular filling pressure | None | |
| Double inlet left ventricle, transposition of the great arteries, pulmonary stenosis (Seywoodhay) | AVR | 14 | Male | Not mentioned | Fontan circulation was revised | Alive 15 years after the onset of PLE. |
| Tricuspid atresia (Gras)        | -                   | 7                       | Male | Budesonide, Not effective | MCT-rich diet, melena disappeared after somatostatin administration | None | Refractory PLE even after cardiac transplantation. Died 6 months after transplantation. Remission. Scheduled to undergo fenestration and atrioventricular valve replacement. |
| Right atrial isomerism, single right ventricle, common atroventricular canal, absent pulmonary valve, right pulmonary venous obstruction, severe atroventricular valve regurgitation (1) |                     |                         |     | Not effective | Refractory to heparin and octreotide, Kyuki-kyogai-to (herbal drug), effective | Lowering of ventricular filling pressure, anoxicillin | → |
| HLHS (Current case)             | TVR                 | 7                       | Male | Prednisolone, Not effective | Lowering ventricular filling pressure, low residue diet, heparin anticoagulation | None | Remission. Died 4.4 years after the onset of PLE due to multiple organ failure. |

PLE indicates protein-losing enteropathy; AVSD, atrioventricular septal defect; AVR, aortic valve replacement; MCT, medium-chain triglyceride-enriched diet; HLHS, hypoplastic left heart syndrome; and TVR, tricuspid valve replacement.
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