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CASE REPORT

AJT

Reversal of secondary protein-losing enteropathy after surgical revision of a jejunal Roux-en-Y loop in a patient after liver transplantation

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Secondary protein-losing enteropathy (PLE) is a rare complication following pediatric liver transplantation (LT), mostly related to venous outflow obstruction of the liver. Here, we discuss a thus far unknown cause of secondary PLE following pediatric LT. A 7-month-old boy underwent LT with biliary anastomosis using a Roux-en-Y jejunal loop. Eleven months later he developed PLE. Routine diagnostic workup was negative. No hepatic outflow obstruction was detected during catheterization. Although the hepatic venous pressure gradient was slightly increased (10 mm Hg), there were no clinical signs of portal hypertension. Albumin scintigraphy with specific early recordings suggested focal albumin intestinal entry in the jejunal Roux-en-Y loop. Local bacterial overgrowth or local lymphangiectasia, possibly due to (venous) congestion, was considered. Treatment with metronidazole did not improve albumin loss. Next, surgical revision of the jejunal Roux-en-Y loop was performed. The explanted loop contained a small abnormal area with a thin hyperemic mucosa, near the former anastomosis. Histopathological analysis showed changes both in the blood vessels and the lymphatic vessels with focal deeper chronic active inflammation resulting in congestion of vessels, hampering lymphatic outflow leading to lymphangiectasia and patchy distortion of lymphatic vessels. Following surgical revision, secondary PLE disappeared, up to now, 1.5 year post revision.

KEYWORDS
clinical decision-making, clinical research/practice, liver transplantation, liver transplantation/hepatology, split

1 | INTRODUCTION

Protein-losing enteropathy (PLE) is defined by an abnormally rapid loss of serum proteins into the gut lumen. Within the normal intestinal mucosa the vast majority of intravascular proteins are transported from the arterial capillaries to the capillaries of the portal venous system. The albumin that slowly leaks from the plasma to the interstitial space is removed by the lymphatic system, which drains via the thoracic duct into the innominate vein and eventually into the superior vena cava. At the intestinal mucosa, epithelial cells present a diffusion barrier between the interstitial space and the gut lumen that prevents leakage of protein into the gut lumen (Figure 1). Based on this physiology, causes of PLE can be classified as follows. First, there can be increased protein supply from the mucosal capillaries into the interstitial space, such as in increased vascular permeability. Second, there can be a decreased

Abbreviations: FIC, familial intrahepatic cholestasis; LT, liver transplantation; PLE, protein-losing enteropathy.

drainage of interstitial protein via the lymphatic system, such as in lymphatic obstruction or elevated lymphatic pressure. Third, damage to the epithelial barrier may cause leakage of interstitial protein in the gut lumen (this can be either in the presence or absence of mucosal erosions).[1,2]

PLE following liver transplantation (LT) is a rare but known complication. There have been only few case reports in both adults and children. Here, we discuss all available reports. The most frequent cause of PLE was outflow obstruction of the liver. Two children (aged 18 months and 10 years at transplantation) developed PLE after LT due to vena cava inferior obstruction.[3] Similarly, a 42-year-old patient developed PLE due to a significant stenosis of the suprahepatic caval anastomosis.[4] Stenosis of anastomosis of the hepatic vein to the inferior vena cava caused PLE in a 2-year-old girl [5] and a 13-year-old girl.[6] Correcting outflow by balloon dilatation of the stenosis was shown to end PLE.[3-6] Also, one report was made of a 57-year-old patient who developed cirrhosis of the liver graft, resulting in PLE due to acquired intestinal lymphangiectasia.[7]

Besides these vascular causes, PLE due to an incisional hernia was reported in a patient transplanted at 52 years of age.[8] Finally, in children with progressive familial intrahepatic cholestasis (FIC) type 1, PLE can develop following LT due to restoration of intestinal bile flow from a normal liver, which aggravates the FIC1 intestinal defect.[9-12]

Here we discuss a case of focal PLE in the jejunal loop following LT that could not be explained by one of these previously reported causes and was successfully treated with a surgical resection.

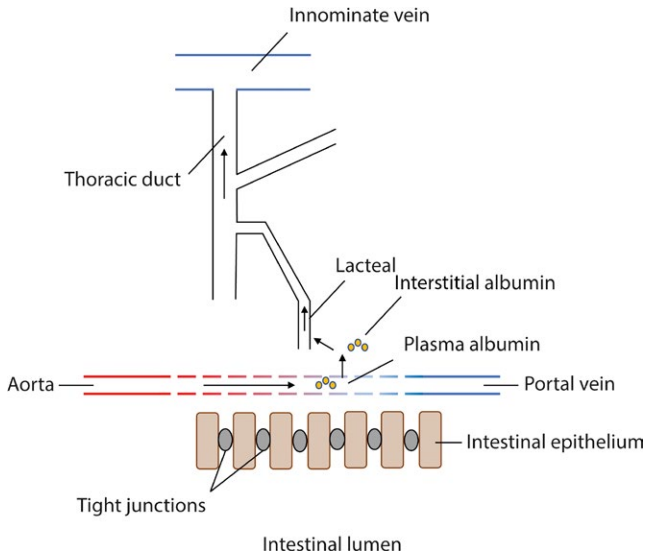

FIGURE 1 Albumin circulation in intestinal tissue. Schematic overview of physiologic albumin circulation through the intestinal vasculature and interstitial space. Albumin that leaks to the interstitial space from the plasma is removed by the lymphatics and transported back to the superior vena cava via the innominate vein. Tight junctions between epithelial cells prevent leakage to the intestinal lumen

2 | CASE DESCRIPTION

A 6-month-old boy was listed for LT because of ornithine transcarbamylase deficiency with frequent metabolic derangements leading to hyperammonemia and encephalopathy. At the age of 7 months, he received a split liver graft (segments 2 and 3) of a donor after brain death. A duct-to-duct anastomosis of the bile duct was not feasible due to the presence of two separate segmental bile ducts of the liver graft and a too large distance to the recipient's bile duct. Therefore, a hepaticojejunostomy was constructed. To this end, the jejunum was cut at 30 cm from the ligament of Treitz. The mesentery was cleaved over sufficient distance, and the first arterial arcade was left intact. A jejunal Roux-en-Y loop of 40 cm was created and retrocolically tunneled for anastomosis to the bile ducts in the liver graft. An end-to-side jejunojejunostomy restored intestinal continuity. Unfortunately, the graft suffered from primary nonfunction/delayed graft function, for which the patient was relisted for high urgency retransplantation, during which period hepatic artery thrombosis occurred. Nine days after the first transplantation, a second transplantation of a split liver graft (segments 2 and 3) of a brain-dead donor was performed. Again, the biliary anastomosis was made by using the existing jejunal Roux-en-Y loop. The resulting anatomy is shown in Figure 2. The postoperative course was uncomplicated except for transient chylous drainage from the abdominal drain. The following months were uneventful, except from a primary Epstein–Barr virus infection, with a good clinical recovery.

However, at the age of 18 months, he quite suddenly developed generalized edema and ascites. A marked hypoalbuminemia (21 g/L) was found and PLE was diagnosed, as fecal alpha-1 antitrypsin levels were markedly increased (up to 10 mg/g, normal value < 2.6 mg/g). Due to PLE, serum Immunoglobulin G levels dropped to 1.9 g/l. The clinical impact was major; he required suppletion (2 gram/kilograms body weight) of albumin intravenously every 2 weeks to limit generalized edema and ascites.

2.1 | Diagnostic workup

Extensive systematic evaluation to find the cause of the patient's PLE was performed.[13] No infectious cause was found. Endoscopy (gastroduodeno/colonoscopy, capsule endoscopy) showed no mucosal injuries and no signs of lymphangiectasia. ^{18}F-FDG positron emission tomography/computed tomography scan showed no signs of posttransplant lymphoproliferative disorder.

As venous outflow obstruction is the most important cause of PLE following LT,[3-6] catheterization was performed, which showed no signs of venous outflow obstruction. Central venous pressure (9 mm Hg in the inferior vena cava) and pressure in the hepatic vein (9 mm Hg) were both normal. The hepatic venous pressure gradient was 10 mm Hg, which was slightly increased, as the upper range of normal is 5 mm Hg.[14] However, we considered the portal hypertension mild as there was no splenomegaly, no sign of esophageal varices on endoscopy, and no

thrombocytopenia (thrombocytes 326 10E9/l) or leukopenia (leucocytes 6.1 10E9/l).

A liver biopsy taken during the same procedure showed some sinusoidal and perivenular fibrosis, central venulitis and perivenular inflammation. These findings were considered to be most likely caused by immunological activity, with rejection being more likely than infection.

The localization of intestinal albumin loss was evaluated using albumin scintigraphy (technetium-99 m labeled albumin). At first, no focal site of protein loss was detected, with the standard dynamic phase 0-30 minutes, followed by a SPECT-CT scan with better 3D information at a standard 120 minutes after tracer injection. We speculated that if focal leakage and luminal spreading of labeled albumin had occurred prior to the SPECT-CT recording phase, a focal

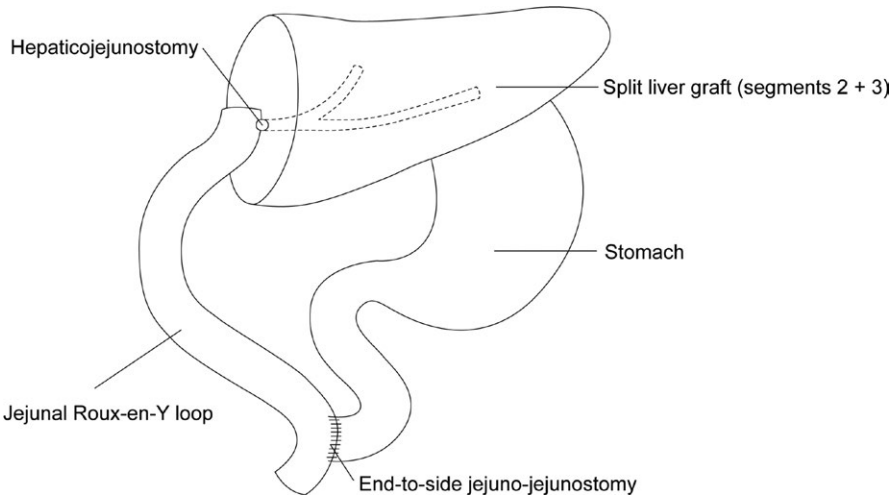

FIGURE 2 Anatomical situation. Following transplantation with a split liver graft (segments 2 and 3), during which the jejunal Roux-en-Y loop was created, the resulting anatomical situation was as shown here

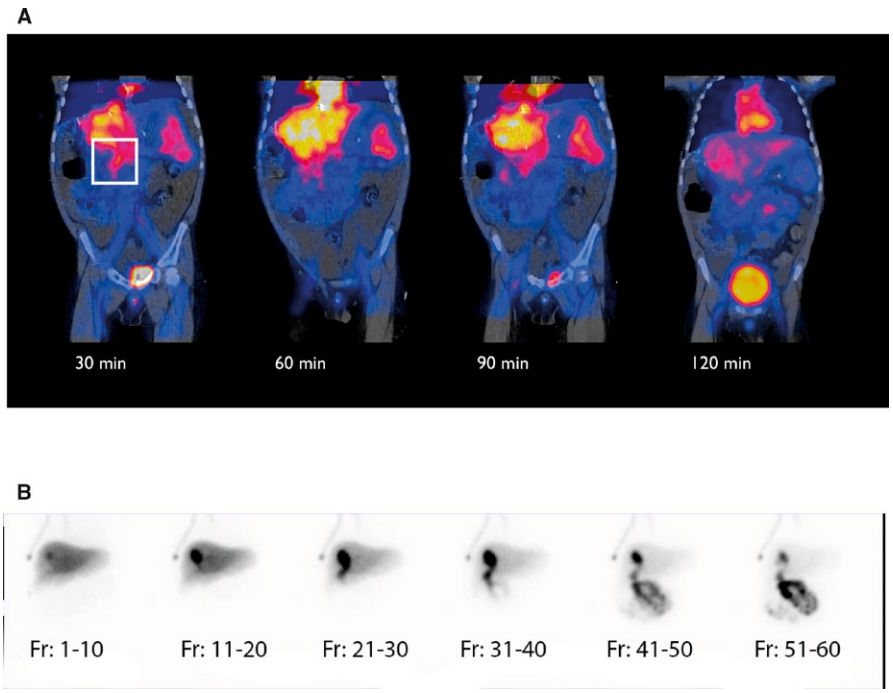

FIGURE 3 Albumin scintigraphy and cholescintigraphy. Albumin scintigraphy is shown in panel A. Immediately after injection of 233 MBq Technetium-99m labeled albumin, dynamic imaging was performed for 30 minutes (60 sec/frame, matrix 128 × 128) using a dual-headed gamma-camera equipped with a low-energy collimator and a CT-scanner (Siemens Symbia T2). SPECT-CT images were recorded at 30, 60, 90, and 120 minutes postinjection (SPECT settings: 15 sec per view, 64 views, attenuation corrected iterative Flash 3D reconstruction with 8 iterations and 16 subsets. CT settings: mAs 30, 110 kV, slice 3 mm). Focal entrance of albumin was observed in the early recordings (boxed area, left tableau). Later recordings showed spread (considered the result of intraintestinal passage) of albumin throughout a larger intestinal area. Panel B depicts cholescintigraphy (26 MBq Tc-99m-Mebrofenin), as a reference for the anatomical relation between liver, Roux loop, and jejunum in our patient. Dynamic recordings immediately after injection were made during 60 minutes with one frame every minute on a dual-headed SPECT-CT camera (Siemens Symbia T2); Fr: 1-10 being the sum of frames from 1 to 10 minutes, Fr: 11-10 from 11 to 20 minutes, and so on

site might have been missed. Therefore, albumin scintigraphy was repeated with specific early recordings (SPECT-CT recordings at 30, 60, and 90 minutes after tracer injection instead of after 120 minutes). Now, we observed focal albumin loss in the intestine, starting as early as within the first 30 minutes (Figure 3A). Therefore, early recordings were pivotal to detecting focal albumin loss; technical details of the scintigraphy are included in the figure legend.

The area was suspected to be the jejunal Roux-en-Y loop, which was supported when comparing the area to a previous cholescintigraphy (technetium-99 m labelled mebrofenin) of the patient (Figure 3B). The albumin scintigraphy and cholescintigraphy showed overlap between the lightened area.

2.2 | Revision of the jejunal Roux-en-Y loop to treat PLE

Possible causes of focal PLE were considered, such as local bacterial overgrowth or local lymphangiectasia. Local bacterial overgrowth is reported as a cause of PLE in adults after a bariatric Roux-en-Y gastric bypass.[15] Treatment with metronidazole did not improve albumin loss, rendering local bacterial overgrowth an unlikely cause of the PLE. As the PLE persisted and the patient's condition was deteriorating, we decided to perform a surgical revision of the jejunal Roux-en-Y loop. There were no signs of an incisional hernia and no torsion of the Roux-en-Y jejunal loop was observed. The jejunal loop (13 cm) was disconnected from the bile duct of the donor liver and completely resected. A new jejunal loop was created. The procedure was uncomplicated. The explanted loop measured 13 × 2.5 cm (Figure 4A), the serosa showed pronounced vasculature and was irregularly red. 0.5 cm from the resection margin was a slightly elevated, intact, yellowish area of 0.6 cm (Figure 4B) with a thin intestinal wall. This elevated area was sampled in total. Histopathological examination showed various vessel-related changes throughout the explanted loop, of which the most remarkable was the patchy lymphangiectasia, as there were focal congested lacteals in the mucosa and an increase in dilated lymph vessels in the whole intestinal wall (Figure 4C,D) with additional patchy distortions (Figure 4E), confirmed in the immunohistochemical stainings with D2-40 and Erg. In addition there were dilated, prominent small and middle large veins spread through the whole intestinal wall but especially in

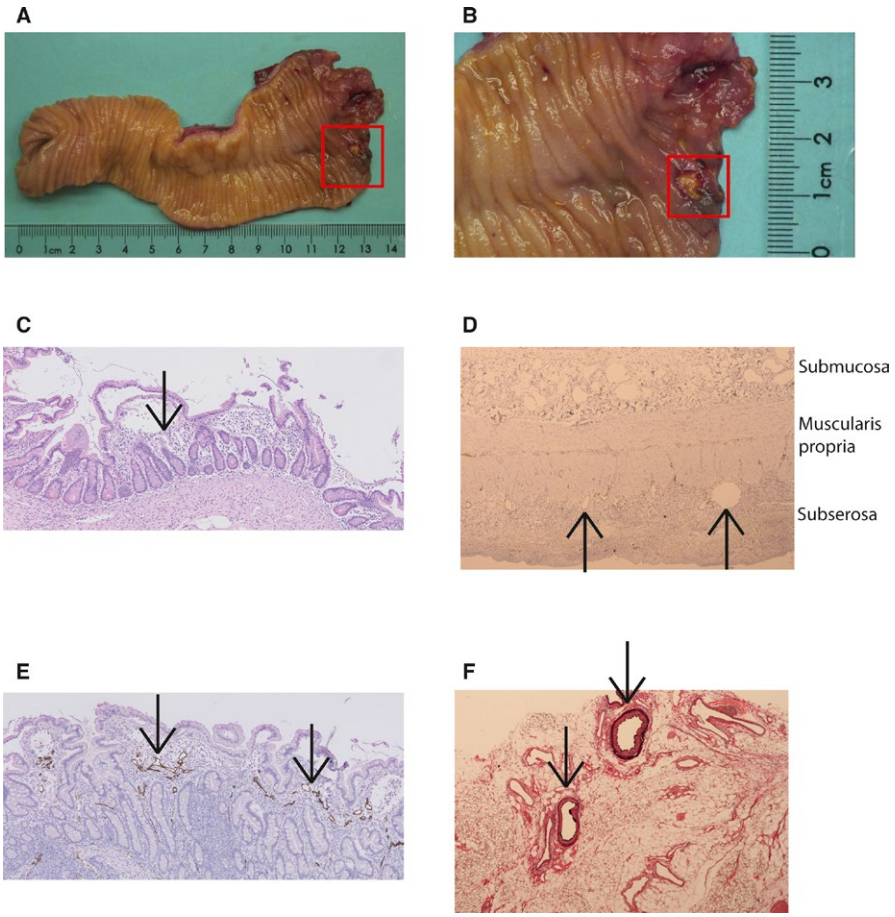

FIGURE 4 Resected jejunal Roux-en-Y loop. Study of the resected jejunal Roux-en-Y loop (A) macroscopically showed a slightly elevated, yellowish mucosal lesion with a thin hyperemic mucosa (B). Histopathological analysis with hematoxylin and eosin stain showed dilated lacteals (arrow) in the lamina propria (C). Lymphangiectasia (arrows) was confirmed with D2-40 immunohistochemistry; dilated lymph vessels were present in the submucosa and subserosa with subserosal active inflammation (D). Focal presence of dilated lacteals and patchy presence of distorted lymph vessels through the intestinal wall were observed (D2-40 immunostain; E). Subserosal blood vessels were prominent and dilated, with units of blood and lymph vessels of different caliber (Verhoeff's stain; F)

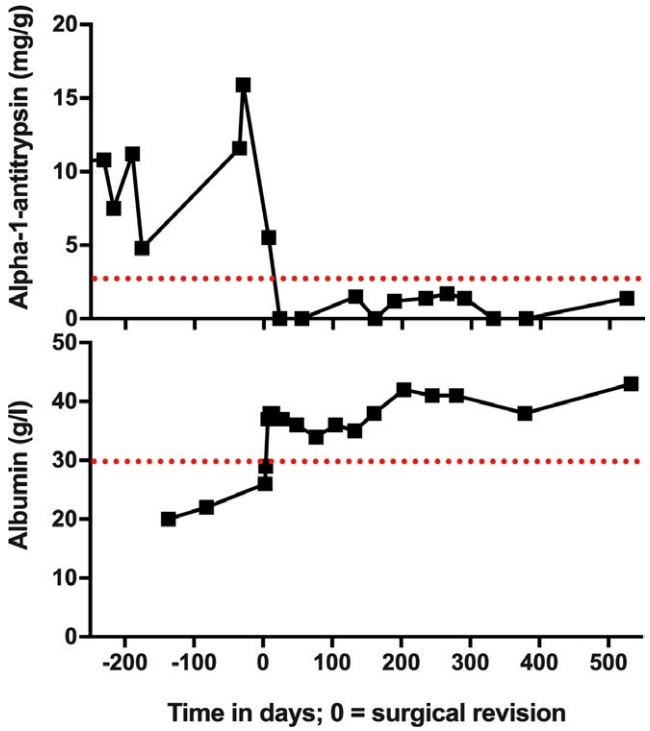

FIGURE 5 Disappearance of fecal Alpha-1-antitrypsin (A1AT) and normalization of plasma albumin following surgical revision of the Roux-loop. Following surgical revision of the Roux-loop fecal A1AT levels normalized (red dotted line: upper limit of normal range) and remained normal up to now, one and a half year following revision. Immediately, plasma albumin levels normalized (red dotted line: lower limit of normal range) as well. Note: prior to surgical revision, albumin was administered every 2 weeks, with 2 gram/kilogram body weight. Therefore, albumin levels during this period do not fully reflect the severity of PLE

the subserosa in units of blood vessels of comparable caliber and dilated lymph vessels (Figure 4F) focally accompanied by (sub)serositis (Figure 4D). The surface epithelium showed no inflammation of dysplasia and in the intestinal wall there was no malignancy. In immunohistochemical staining cytomegalovirus was not detected.

Following surgical revision, PLE disappeared and serum albumin levels remained stable, up to now, 1.5 year post revision (Figure 5). The patient has been in good clinical condition since (Figure 6).

3 | DISCUSSION

PLE following liver transplantation is very rare, and almost all published cases were related to outflow obstruction of the liver. However, in this case report, we did not find an outflow obstruction. PLE was focal, as detected by the use of specific early recordings in albumin scintigraphy. Likely site of protein loss was a small abnormal intestinal area near the anastomosis of the jejunal Roux-en-Y loop. Key histopathological findings were vascular congestion through the whole intestinal wall including both blood vessel and lymphatic vessels with patchy lymphangiectasia and lymph vessel distortion accompanied by focal (sub)serosal inflammation. We hypothesize that focal PLE resulted from an interplay between local factors and a systemic factor, ie, portal hypertension.

Histopathological analysis showed signs of vascular congestion throughout the explanted jejunal loop, presumably due to portal hypertension as measured during catheterization. Portal hypertension in itself rarely leads to PLE, and if so, only in patients with cirrhosis and/or clinical signs of portal hypertension.[1] However, portal hypertension can contribute to PLE, as increased portal vein pressure leads to increased intestinal capillary fluid filtration and increased lymphatic flow, through increased mucosal capillary pressure and the concomitant increase in mucosal interstitial pressure. This may give rise to lymphangiectasia.

Focal intestinal protein can be limited; however, in the case of generalized intestinal lymphangiectasia it may be gross. Here, focal intestinal protein loss likely occurred in the small abnormal area near the former anastomosis. Local factors there included more

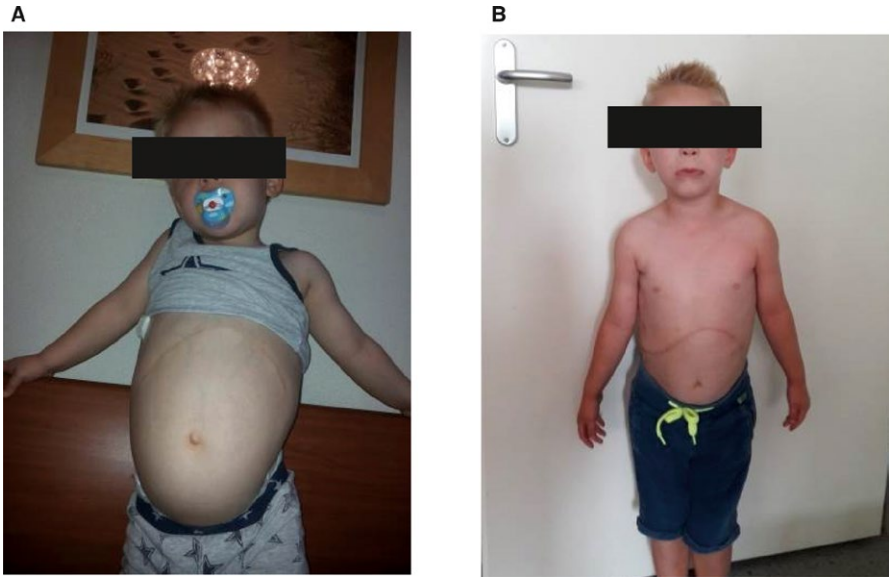

FIGURE 6 Patient photos. Prior to revision of the Roux loop, the patient had extensive ascites (A), following revision, ascites completely resolved (B). Images reproduced with patient family consent

pronounced lymphatic changes and inflammation. Lymph vessels were contorted, as can be seen in young vessels. This may reflect lymphangiogenesis and lymphatic vessel remodeling, as may occur in inflammation, which can also cause lymphatic dysfunction.[16] As another contributing factor, vascularization near an intestinal anastomosis can be hampered, and disturbances in microcirculation may result in inflammation, up to the level of chronic ulcers, as has been reported in patients with short bowel syndrome following resection of an intestinal segment.[17] In our patient, histopathological signs of inflammation and vascular congestion of both blood vessels and lymph vessels were noted and vascular permeability had likely been increased. Though changes were not up to the level of an anastomotic ulcer, it is relevant to consider that such ulcers are reported causes of PLE.[18]

In conclusion, as surgical revision of the Roux-en-Y loop successfully treated PLE up to now (1.5 years later), local factors must have been relevant. Regarding systemic factors, mild portal hypertension remained, but as a sole factor, as discussed, this is not expected to result in PLE.

Permission for publication was given by the family.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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