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Devastating outflow obstruction after pediatric split liver transplantation

Sakamoto S, Nakazawa A, Shigeta T, Uchida H, Kanazawa H, Fukuda A, Karaki C, Nosaka S, Kasahara M. Devastating outflow obstruction after pediatric split liver transplantation.

Abstract: HVOO is a rare complication after pediatric LT, which may lead to graft failure. There are various causes of HVOO, such as mechanical anastomotic obstruction and SOS. A 10-month-old female underwent split LT from a deceased donor for ALF. Her postoperative course was uneventful. However, her liver function suddenly deteriorated a month later. A liver biopsy revealed centrilobular injury, and D-US suggested outflow obstruction. Venography was performed to reveal hepatic venous narrowing inside the graft. She received another graft from a living donor because of progressive graft failure in spite of successful venoplasty with stent insertion. The macroscopic findings of the explanted graft did not show an anastomotic stricture of the hepatic vein, although the pathological findings revealed necrosis of the first graft due to SOS. SOS might cause severe consequences with concomitant mechanical outflow obstruction after pediatric LT.

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Acute hepatic venous outflow obstruction after LT can present as an acute Budd–Chiari syndrome (1). Mechanical obstruction caused by anastomotic occlusion or stricture of the hepatic vein is often suspected as a common cause. Numerous technical innovations in LT have been achieved to avoid such a vascular complication (2). SOS, previously named VOD, is clinically characterized by jaundice, hepatomegaly, and ascites and occasionally evolves to liver failure in severe cases (3). Although SOS has been reported to occur as a well-known complication after chemo-irradiation conditioning regimens during bone marrow transplantation (4), the incidence of SOS after LT is low, occurring in only 1.9% of cases; however, the outcome is quite poor (5). Prompt management is crucial for the affected patients to survive, although the severe type of SOS presents a devastating clinical course, which may lead to graft failure (6). This report presents a pediatric case with a severe outflow obstruction possibly due to both mechanical obstruction and subclinical SOS after split LT.

Abbreviations: ACR, acute cellular rejection; ALF, acute liver failure; D-US, Doppler ultrasound; GRWR, graft to recipient body weight; HVOO, hepatic venous outflow obstruction; LT, liver transplantation; SOS, sinusoidal obstruction syndrome; TIPS, transjugular intrahepatic portosystemic shunt; VOD, veno-occlusive disease.

Case

A 10-month-old female (body weight: 7.3 kg), with ALF of unknown etiology, underwent split LT by receiving a left lateral segmental graft from a deceased donor. The donor was relatively old, 65 yr, with a mild steatotic liver. The operation was uneventful with cold ischemic time of approximately seven h. The graft weight was 294 g; thus, the GRWR was 4.03%, and partial skin closure was required to close her abdomen. Tacrolimus with an appropriate

trough level and steroids were used for the initial immunosuppression. Her liver function had become stable for a month after her first LT, except one episode of a slight increase of liver enzymes, which was managed with an increased dosage of tacrolimus. D-US, which was routinely performed twice daily for the first two wk and then once every day, did not show any vascular complications, including the documentation of a pulsatile hepatic venous outflow waves. However, her liver enzymes suddenly increased and her clinical condition deteriorated (Table 1). A liver biopsy revealed centrilobular injury (Fig. 1a), and D-US revealed a limited portal venous flow and a flat hepatic venous flow with dilated intrahepatic veins, which indicated hepatic outflow obstruction. Venography was promptly performed to reveal narrowing of the hepatic venous outflow inside the graft close to the hepatic venous anastomosis and required stent insertion (10 mm × 2.5 cm; Boston Scientific, Natick, MA, USA; Fig. 2), which effectively improved portal venous flow (Fig. 3). Although liver support therapy, including continuous hemodiafiltration and plasma exchange, and steroid pulse therapy were immediately initiated after the successful venoplasty, her liver function rapidly deteriorated. She underwent retransplantation by receiving a left lateral segmental graft (GRWR; 2.4%) from her mother. Her explanted graft was 381 g, which was enlarged to approximately 1.3 times larger than the original graft weight. The stent was properly placed at the narrowing site of the left hepatic vein close to the hepatic venous anastomosis, and no macroscopic anastomotic stricture or thrombosis of the hepatic vein was found. The pathological findings showed massive necrosis of hepatocytes, and fibrous obliterative lesions accompanied with organized microthrombi were found in some of the central venules, which were compatible with SOS (Fig. 1b). Her post-transplant course was uneventful, and she was doing well with a stable liver function six months after her second LT.

Table 1. Laboratory data at the onset of acute outflow obstruction

POD after DDLT	AST (IU/L)	ALT (IU/L)	LDH (U/L)	TB (mg/dL)	PT-INR
24	58	49	187	0.79	
26 (on the morning)	468	247	1117	1.38	
26 (after 12 h)	16170	6680	17560	1.81	1.74
27	12420	2640	7520	1.8	2.3
28	2180	1028	918	2.86	1.8
29	675	432	364	6.33	2.21
30	271	291	232	7.03	2.25
31 (before retransplantation)	149	210	243	7.86	2.09

AST, aspartate amino transferase; ALT, alanine transaminase; DDLT, deceased donor liver transplantation; LDH, lactate dehydrogenase; POD, postoperative day; PT-INR, prothrombin time–international normalized ratio; TB, total bilirubin.

Discussion

Hepatic venous outflow obstruction after LT can be caused by mechanical outflow obstruction and SOS, both of which are completely different from each other in pathogenesis. The diagnosis of mechanical outflow obstruction can be made by radiological examinations. In contrast, the diagnosis of SOS can be confirmed histologically on the basis of fibrous obliterative lesions in the hepatic veins, which are accompanied by centrilobular injuries (7), and SOS is often not suspected on clinical grounds. Furthermore, Sebagh et al. (5) noted that the histological diagnosis of SOS may be difficult and hazardous, and liver biopsies may have a large false-negative sampling error, because terminal hepatic veins do not show uniform involvement with SOS. A liver biopsy revealed centrilobular injury in the current case, which might suggest the presence of SOS, although the finding of D-US clearly

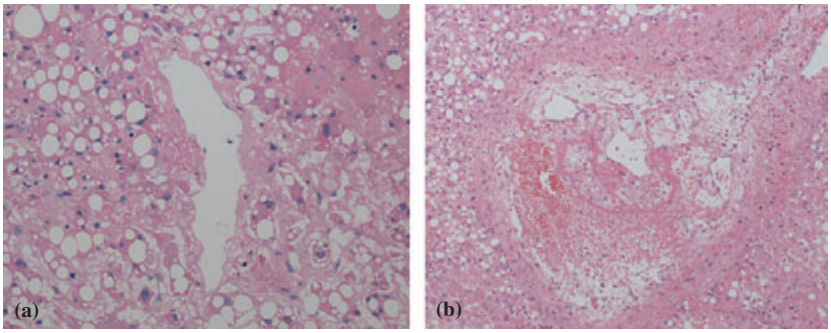

Fig. 1. The pathological findings of a needle liver biopsy (a) showed centrilobular injuries, including severe hepatocyte degeneration and necrosis with steatosis. The pathological findings of the explanted graft (b) showed massive necrosis of hepatocytes with fibrous obliterative lesions in some of the central venules accompanied with organized microthrombi.

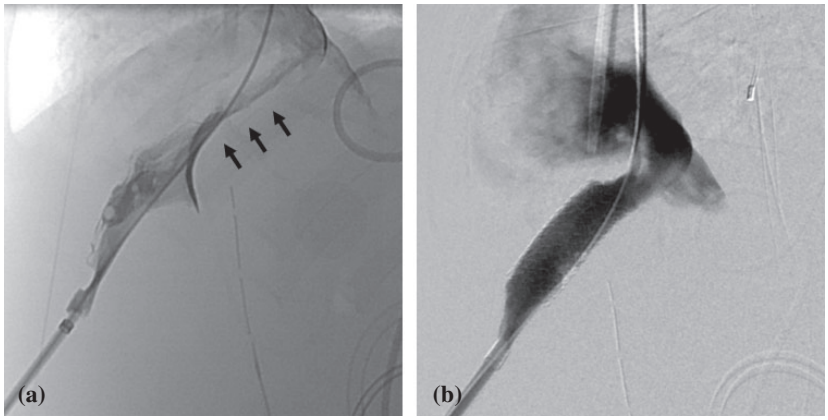

Fig. 2. Venography (a, lateral view) revealed a narrowing of the hepatic venous outflow inside the graft close to the hepatic venous anastomosis (arrow). Stent insertion (b, lateral view) successfully improved the hepatic venous outflow.

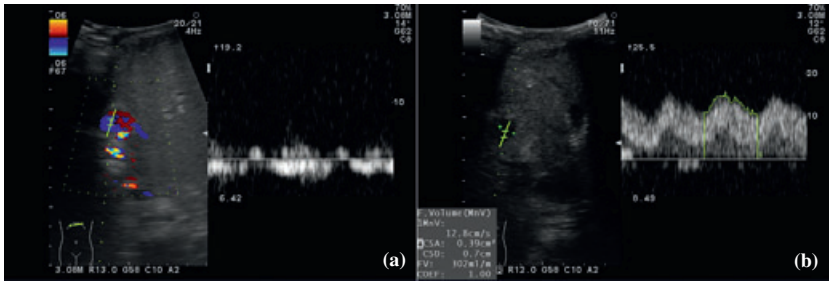

Fig. 3. The findings of D-US before (a) and after (b) the stent insertion revealed the improvement of portal venous flow.

indicated mechanical outflow obstruction, which was confirmed by venography.

Anastomotic occlusion or stricture of the hepatic vein is generally associated with technical issues of hepatic venous reconstruction, although the size, shape, and orientation of the type of graft may predispose kinking of the hepatic venous outflow, especially when using a segmental graft for smaller children (1). Venography showed narrowing of the hepatic venous outflow in the current patient, close to, but not exactly at the anastomotic site. Rapid enlargement of the graft, which was possibly triggered by SOS, may have suddenly induced bending and stretching of the hepatic venous outflow. Moreover, the recipient received a relatively large graft in her small abdominal cavity, which could have compromised the hepatic outflow because of compression.

SOS after solid organ transplantation is a recognized condition in the context of azathioprine toxicity (8). In the report of the largest series of SOS after LT, most of the patients with SOS had an episode of ACR before or at the time of SOS, and the authors suggested that SOS might have an association with cellular rejection with an endothelialitis-induced damage to the centrilobular venous wall (5). The current patient had an episode of a slight increase of liver enzymes a wk before a rapid deterioration of her clinical conditions. Although a liver biopsy was not performed, it is speculated that ACR or a pathological feature indicative of SOS, such as centrilobular endothelialitis, might have already occurred at that point. On the other hand, the etiology of ALF in the current patient remains unknown in spite of precise pretransplant examinations. The outcome of LT for ALF of unknown etiology in smaller children is poor, and centrilobular injuries have often been simultaneously observed with ACR in the liver biopsy specimens at the time of rapid deterioration of liver functions after LT (9). Although these pathological findings might be recognized as a manifestation of rejection, the recurrence of the original disease after LT could not be ruled out as a cause of graft failure. Shimojima et al. (10) described that unique vascular obstructive changes like SOS occurred in native livers and transplanted allografts in infants after LDLT for cryptogenic fulminant hepatic failure. The pathological findings compatible with SOS in the current patient might be similar to their findings, although the pathogenesis of centrilobular injuries remains unknown.

The effectiveness of medical and/or radiological treatment has been previously reported for severe type of SOS. Defibrotide, a polydeoxyribonucleic acid with pro-fibrinolytic and antithrombotic properties, can provide promising results, although the response rate is only about 40% (11). A TIPS is another therapeutic option (12). Campos-Varela et al. (13) summarized seven LT recipients of TIPS-treated SOS and showed that all but one recipient survived, although two required retransplantation and histological resolution of SOS was observed in only one case. In addition, all of the TIPS-treated recipients were adults, and TIPS is technically difficult in small children, as was the situation in the aforementioned case.

Most of the previously reported cases with SOS after LT were adults (5, 6, 12, 13, 14, 15). To the best of our knowledge, only one case demonstrating SOS to occur after LT in a small child has been previously reported (16). Adult patients with SOS tend to show a gradual deterioration over a couple of months. In contrast, the pediatric case with SOS presented with early graft failure several days after undergoing the first LT (16). This case demonstrated a number of similarities with our current case, such as a high GRWR (3.9%), an enlarged explanted graft (1.7 times larger than the original graft weight), and a decreased portal vein flow during the clinical course. As a matter of speculation, rapid enlargement of the graft due to SOS might therefore compromise the hepatic blood flow because of compression, and this phenomenon may be one of the characteristic findings of small children with SOS after LT.

It is worthy of note that both mechanical outflow obstruction and SOS occurred concomitantly in the current case, and the persistent severe type of SOS consequently led to graft failure in spite of prompt management of the mechanical outflow obstruction. SOS should be considered for the cases with acute hepatic venous outflow obstruction after LT.

Authors' contributions

S.S.: study design and writing of the article; A.N.: critically revising the article for pathological content; T.S., H.U., H.K., A.F., and C.K.: collection of data; S.N.: critically revising the article for radiological content; M.K.: study design and critically revising the article for surgical content.

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