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Case Report

Intractable ascites without mechanical vascular obstruction after orthotopic liver transplantation: etiology and clinical outcome of sinusoidal obstruction syndrome

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Abstract: Intractable ascites after orthotopic liver transplantation (OLT) is a relatively rare complication. However, it often takes a life threatening course, which requires re-transplantation. In previous studies, several reports gave hepatic sinusoidal obstruction syndrome (SOS) as one of the causes of refractory ascites. However, the detailed etiology of SOS after OLT and its association with clinical consequences remain unclear because there have been few studies to date. We report two recent cases with rapidly progressive refractory ascites associated with SOS, following completely different clinical courses. In case 1, the first episode of acute allograft rejection triggered SOS and subsequent intractable ascites, while the second acute rejection worsened his clinical status. A transjugular intrahepatic portosystemic stent-shunt (TIPS) was placed and this procedure resulted in complete disappearance of ascites and of renal dysfunction. In contrast, refractory ascites in case 2, who had neither rejection nor mechanical outlet obstruction, worsened despite TIPS stent placement, and re-transplantation was necessary. We speculate that the pre-existing diseased liver of the cadaver donor caused this serious complication, necessitating a second graft.

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Key words: glutathione depletion – intractable ascites – liver transplantation – sinusoidal obstruction syndrome – transjugular intrahepatic portosystemic shunt

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Postoperative ascites is one of the common complications of orthotopic liver transplantation (OLT). Although refractory ascites is a relatively rare post-OLT complication, persistence of a large amount of ascites after OLT is one of the ominous signs possibly heralding graft failure. Several reports concerning refractory ascites after OLT have been published, and multiple etiologies of this complication after OLT have been suggested in these reports: mechanical problems include technical failure of vascular anastomoses, metabolic disorders, and lymphatic leakage caused by surgical dissection. Hepatic sinusoidal obstruction syndrome (SOS), previously named veno-occlusive disease (VOD), of the allograft is also one of the causes of refractory ascites and can take a life threatening course. At present, it is assumed that this complication is strongly associated with acute allograft rejection.

Table 1. Donor–recipient human leukocyte antigen (HLA) typing in case 1

	HLA-A	HLA-B	HLA-DRB1
Donor	A2,30	B39,18	DR15,11
Recipient	A26,26	B27,38	DR01,13

However, the actual mechanism underlying rapid progression of intractable ascites associated with SOS remains unknown. We present herein two cases with rapidly progressive ascites associated with SOS after OLT. The etiology of SOS after OLT and its clinical significance are also discussed.

Case 1

A 67-yr-old man underwent cadaver donor liver transplantation with standard techniques including cavocaval anastomosis for end-stage liver disease secondary to alcoholic hepatitis, complicated by massive ascites and esophageal varices. His human leukocyte antigen (HLA) typing was fully mismatched with that of the donor for A, B, and DRB1 (Table 1). His weight dropped from 82 kg to 72.6 kg just after LT because of the removal of a large amount of ascites. The immunosuppression regimen consisted of triple therapy with tacrolimus, mycophenolate mofetil, and steroids. His postoperative course was uneventful, but serum laboratory studies at postoperative day (POD) 11 revealed elevated liver function values: total bilirubin, 90 μmol/L (2–17 μmol/L); γ-glutamyl transpeptidase (GGT), 262 IU/L (7–32 IU/L); aspartate aminotransferase (AST), 54 IU/L (17–27 IU/L); and alanine aminotransferase (ALT), 105 IU/L (11–26 IU/L). Histologic examination by percutaneous needle biopsy the following day revealed a lymphocytic portal inflammatory infiltrate, and endothelial inflammation of the portal and centrilobular veins. These findings correspond to a rejection score 3 in 10 according to the European grading system for acute liver allograft rejection (1–3), i.e., acute mild rejection. On ultrasound at this time, the portal and hepatic veins, the hepatic artery, and inferior vena cava were all patent. Liver function improved rapidly following the increased dose of tacrolimus. While ascites appeared after this episode and gradually increased despite amelioration of liver dysfunction, he was discharged on POD 26, because his general condition including allograft function was good, and the ascites was tolerable. On POD 61, he was readmitted because of remarkable increased ascites with a 7.6 kg weight gain (10.2%). A massive amount of ascites (10.3 L) was drained via puncture, and he was discharged as his liver function remained stable. On outpatient follow-up (POD 180), laboratory studies for allograft function demonstrated the elevations of AST, ALT, GGT, and total bilirubin to 207 IU/L, 241 IU/L, 208 IU/L, and 24 μmol/L, respectively. A transjugular liver biopsy was required because of the reappearance of massive ascites. The histology showed some sinusoidal dilatation, and liver cell plates had collapsed because of perisinusoidal fibrosis with fibrous septa (Fig. 1B). These findings have not been just observed in pre-transplant donor liver (Fig. 1A). In addition, the hepatic venous pressure gradient (HVPG) was significantly elevated

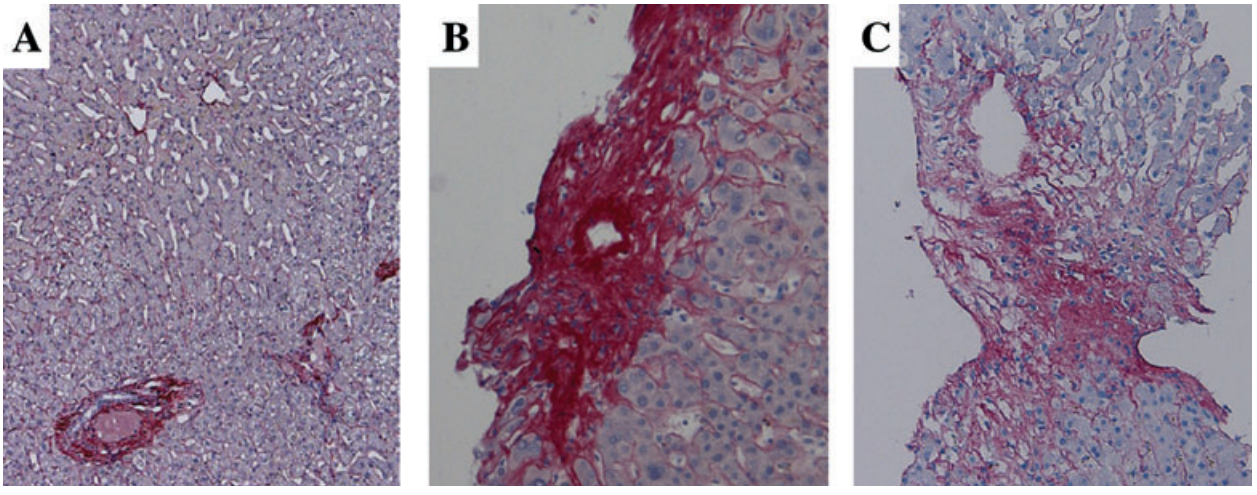

Fig. 1. Histologic appearance of case 1. (A) Donor liver before procurement (sirius red, original magnification ×40). (B) The second biopsy showed perisinusoidal fibrosis with fibrous septa and sinusoidal dilatation (sirius red, original magnification ×200). (C) Centrilobular perisinusoidal fibrous change was seen on follow-up biopsy after disappearance of ascites in response to TIPS placement (sirius red, original magnification ×40).

(21 mmHg). Liver function, nevertheless, improved rapidly with resumption of the discontinued corticosteroids. Two wk after this episode, he presented with severe abdominal distention and slight dyspnea, but his symptoms abated with drainage of 7.7 L of ascites. He again presented, however, to the emergency room two wk later with severe abdominal pain because of massive ascites, which had produced a left inguinal hernia. Laboratory results demonstrated elevation of GGT to 139 IU/L, and renal dysfunction [creatinine level: 132 μmol/L (44–80 μmol/L)]. The patency of all hepatic vessels was confirmed, and cardiac congestion was ruled out by ultrasonography. A transjugular intrahepatic portosystemic shunt (TIPS) stent (7 cm × 10 mm, Viatorr Gore, Flagstaff, AZ, USA) was placed on POD 221. The patient's clinical status slowly improved starting from the second day after the procedure, and he progressed more favorably after discharge from hospital. Twenty-one months after TIPS placement, the patient remained in excellent general condition without reappearance of ascites, while follow-up allograft biopsy showed persistence of far-reaching perisinusoidal fibrosis with sinusoidal dilatations (Fig. 1C).

Case 2

The patient was a 58-yr-old female who underwent OLT for hepatocellular carcinoma with hepatitis C-associated end-stage liver disease. Her immunity for cytomegalovirus (CMV) infection was serologically negative. The donor was a 75-yr-old woman with seropositive status for CMV, who had been declared brain dead after a stroke. The donor had been medicated for many years for treatment of systemic hypertension and hypercholesterolemia. OLT was performed by the standard caval replacement procedure. The cold ischemic time was six h 45 min. Wedge biopsy of the donor liver just before procurement, without a fresh-frozen specimen, revealed 30% steatosis and centrilobular perisinusoidal fibrosis (Fig. 2A). The induction immunosuppressive therapy consisted of cyclosporine, mycophenolate mofetil, and a prednisone taper to a dose of 20 mg. However, tacrolimus was substituted for cyclosporine from POD 8 because of persistently high serum liver function test values since OLT and the appearance of slight convulsions of the extremities. Prophylactic intravenous ganciclovir was postoperatively administered for the CMV seropositive liver graft. The gradually rising liver function test values peaked on POD 9: AST, 90 IU/L; ALT, 90 IU/L; total bilirubin, 280 μmol/L; GGT, 871 IU/L; and alkaline phosphatase (ALP), 192 IU/L (40–120 IU/L). Liver biopsy showed only moderate cholestasis with no signs of acute rejection. By the fifth wk, the weight gain caused by slight hemorrhagic ascites became evident day by day, while the liver function continued to improve. Ultrasound showed normal flow in the portal, arterial, and hepatic veins of the allograft, showing neither venous outlet

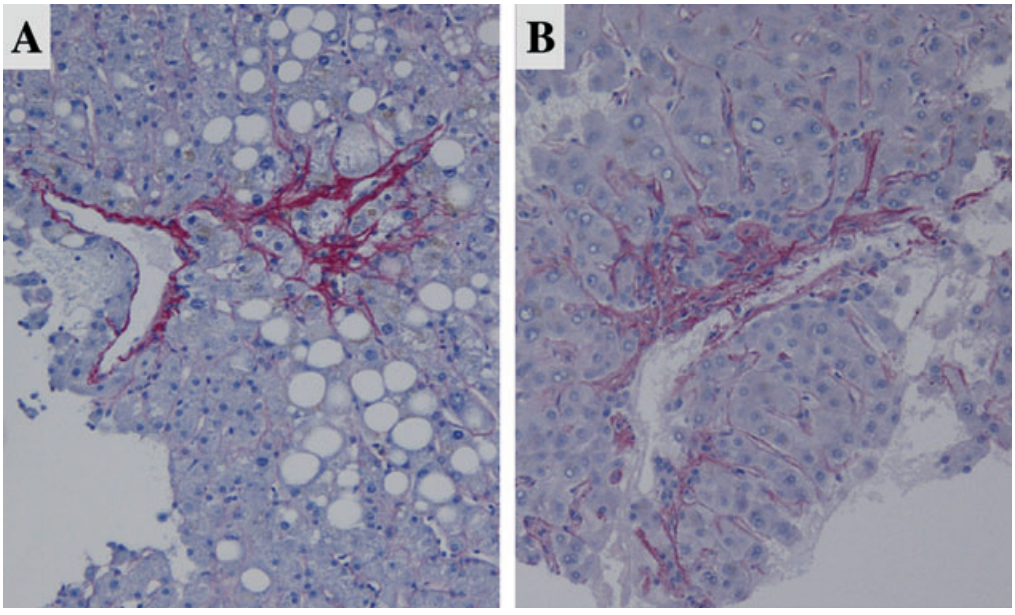

Fig. 2. Histologic appearance of case 2. (A) Donor liver showing 30% macrovesicular steatosis and perisinusoidal fibrosis in the centrilobular area (sirius red, original magnification ×100). (B) Second biopsy after orthotopic liver transplantation showing moderate perisinusoidal fibrosis with obliteration of a centrilobular vein (sirius red, original magnification ×200).

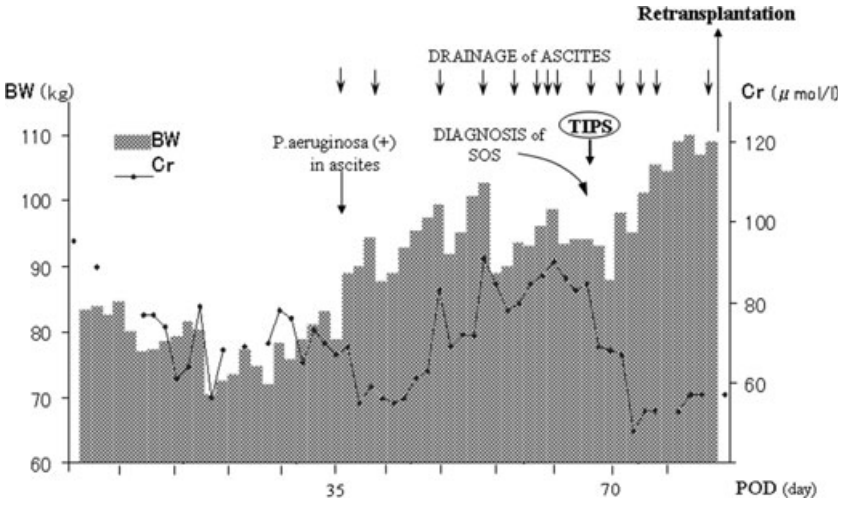

Fig. 3. Clinical course of case 2.

obstruction nor splenomegaly. Bacterial examinations of ascitic fluid on POD 39 revealed *Pseudomonas aeruginosa*, which disappeared after one wk of intensive intravenous administration of antibiotics. The ascites persisted despite recovery from the bacterial infection and all medical treatments were aimed at decreasing ascites. Ultimately, she had a 10-kg weight gain. The patient was forced to depend on repeated paracentesis. On POD 62, the concentrations of serum AST, ALT, GGT, total bilirubin, and ALP rose again to 87 IU/L, 70 IU/L, 1065 IU/L, 20 μmol/L, and 325 IU/L, respectively. A liver biopsy via the transjugular approach revealed complete obliteration of some centrilobular veins associated with perisinusoidal fibrosis (Fig. 2B). Fibrous and inflammatory changes in the portal area were minimal, and there was no endothelialitis. HCV- and CMV- ribonucleic acid (RNA) identified with the reverse transcription polymerase chain reaction (PCR) after OLT were both undetectable throughout her clinical course. These clinical and pathologic findings strongly suggested SOS, while HVPG was modest (9 mmHg). A TIPS stent (5 cm × 10 mm, Viatorr Gore) was placed on POD 68 because renal dysfunction had developed due to the intractable ascites. Although there were temporary improvements in the massive ascites and renal dysfunction after this procedure, her status soon deteriorated resulting in even greater weight gain than during the previous period. Neither hepatic vein obstruction nor TIPS stent obstruction was seen on ultrasound. Her weight gain peaked at 35 kg (46.7%) and she developed bilateral pleural effusions (Fig. 3). She was listed as a candidate for emergency transplantation, and on POD 82, the second OLT was performed. The pathologic study of the explanted allograft revealed striking bridging fibrosis between centrilobular veins and the centrilobular portal space. Some centrilobular veins had been totally replaced by a fibrous mass (Fig. 4A). Several portal venules showed remarkable multiplications with fibrous change, indicative of severe portal hypertension (Fig. 4B).

Discussion

In the early postoperative period of OLT, slight to moderate amounts of ascites are often observed, just as often occurs after other major liver surgeries. Such ascitic fluid usually disappears within several days. It rarely progresses to a serious complication requiring intensive treatment. Even though rather persistent ascitic fluid can unexpectedly develop, it does not cause rapid deterioration of patient's clinical status within a few days. It is likely therefore that postoperative ascites after OLT will attract little attention. In the preoperative cirrhotic state of the liver transplant patient, severe sinusoidal portal hypertension causes arterial hypotension because of decreased peripheral vascular resistance, high cardiac output, hypervolemia, and worsening renal sodium and water retention, as intractable ascites progresses. This state persists even after OLT, and denervation of the graft, which is characteristic of OLT, leads to hepatic artery vasodilatation. In addition, pre-existing splanchnic hyperemia associated with portal hypertension persists in nearly all cases, and furthermore, transection of numerous dilated lymph vessels around the hepato-duodenal ligament increases this amount of fluid leakage. Consequently, systemic hemodynamic derangement remains in the early post-transplant period. However, the graft usually adapts well to this condition eventually. The elevated cardiac output,

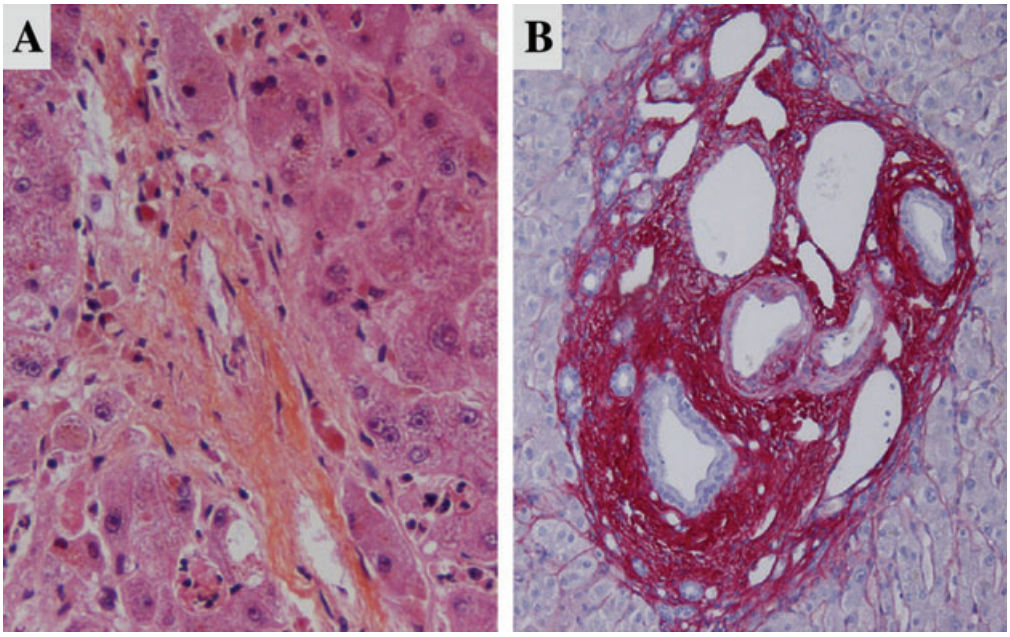

Fig. 4. Explanted first allograft of case 2. (A) A centrilobular vein has nearly been replaced by fibrous tissue (hematoxylin and eosin, original magnification ×200). (B) Portal veinopathy: multiple sections of a portal vein branch, in the portal tract, can be seen (sirius red, original magnification ×100).

aldosterone, plasma renin, and glucagon levels drop to near-normal values two wk after OLT (4). Therefore, in most cases, long-lasting ascites after OLT is not complicated via this circulatory regulation.

The unexpected refractory ascites occurs, however, in a small subset of liver transplant patients. Several authors have reported postoperative hepatic venous outlet obstruction in OLT associated with venous thrombosis, kinking and so on, to be among the major causes of massive ascites. This complication frequently results from surgical procedures such as the piggy-back technique or anastomosis using orifices mismatched in size. Disturbed graft venous drainage leads to portal hypertension, finally producing over-ultrafiltration of the peritoneum (5–8).

Herein, we present two cases with refractory ascites that had not resulted from mechanical outlet obstruction, but rather were caused by SOS. SOS was first described in a Jamaican child by Jelliffe et al. in 1954 (9), replacing the previously named veno-occlusive disease (VOD). A considerable number of studies on SOS have since been conducted on recipients of hematopoietic stem cell transplantation (SCT). In the solid organ transplantation setting, SOS after kidney and liver transplantations were first reported as complications of azathioprine hepatotoxicity in 1982 (10) and in 1991 (11), respectively. Only a few articles have since been published because SOS after OLT is relatively rare, approximately 2% of liver transplant patients according to a previous study (12). The analysis in this report was however worked out on the grounds of histopathological determination, and the details of the clinical symptoms were not taken into consideration when reaching the diagnosis. In most of the other intrinsic liver diseases, portal hypertension occurs in a late stage of the disease as a representation of parenchymal failure. In SOS, however, the symptoms associated with portal hypertension are a feature of the disease itself, and severe damage of the parenchyma is a secondary phenomenon. The diagnostic criteria from the Seattle and Baltimore groups manifest it well, and today, they are cited to diagnose SOS on clinical grounds. Although the criteria of two groups are similar, the Baltimore criteria are slightly more rigorous and represent a worse outcome than that of the Seattle group. In the following investigation, all patients except one satisfied only Seattle criteria, namely jaundice and unexplained weight gain, and it was suggested that the remaining signs, namely tender hepatomegaly and/or ascites, are a vital indicator for the prognosis of the disease (13). In the present study, our two cases both fulfilled the Baltimore criteria, and particularly, the weight gain caused by the marked ascites, which appeared in the early period of the process.

Histopathologically, the cardinal feature of SOS is the injury of sinusoidal lining cells resulting in the disruption of the liver circulation.

The involvement of the hepatic venules is not an essential prerequisite (14, 15). Following the endothelial cell damage, red blood cells leak into the Disse's spaces, thereby producing fibrin deposition, and basement membrane formation and loss of fenestrations caused by fibrous tissue lead to ischemia of hepatocytes, resulting in necrosis. This process within and outside the venular lumina can lead to complete venular obliteration; accordingly, various pathologic features are characteristic of different phases of the disease (16). This variability often complicates making the diagnosis. It is currently recognized that the incidence of SOS after OLT is frequently associated with acute allograft rejection. However, not all patients with acute allograft rejection after OLT develop SOS, and there has been little study of the specific rejection mechanisms or factors which contribute to SOS. Accordingly, the exact cause of SOS is still obscure, due in part to various predisposing factors. We have presented herein two patients who had completely different backgrounds and clinical courses.

In case 1, the first acute rejection occurred in the early post-transplantation period (POD 11). In contrast to the rapid improvement of liver function in response to increasing the tacrolimus dose, this episode triggered intractable ascites. At the second rejection on POD 180 after corticosteroids discontinuation, allograft biopsy, some days after second steroid administration, demonstrated findings of SOS. In human liver grafts, HLA compatibility is less important than with other organ transplantations in terms of rejection. Indeed, rejections in this case were neither frequent nor severe despite full-mismatch compatibility with the donor. However, major histocompatibility complex (MHC) antigens are induced on vascular endothelial cells of portal vessels and sinusoids during rejection. In particular, HLA class I antigens are major transplantation antigens, functioning as binding site for cytotoxic T cells, because most constitutive class II positive cells in the graft, i.e., Kupffer and dendritic cells, have a limited life span and will be replaced by recipient type cells (17, 18). Furthermore, certain monoclonal antibodies are known to be reactive only with sinusoidal lining cells, i.e., they do not react with endothelial cells of portal and central veins, or with arterioles (19). Thus, endothelial cells from different anatomical compartments of the liver have different immunologic functions. Hepatic immunoreactivity is thus quite intricate, reflecting the diverse types of hepatic functional cells. The causative immune response in cases with acute allograft rejection, which triggers SOS, remains to be determined.

In case 2, there was no evidence of acute rejection during the progression of significant ascites. However, several other causative factors subsisted in this patient. She was positive for serum anti-HCV antibody. HCV-related cirrhosis is currently the leading indication for OLT, and the recurrence of HCV frequently occurs after OLT, with more than 90% of allografts demonstrating HCV-induced histologic damage within three yr post-OLT (20, 21). Furthermore, hepatocellular injury can arise from an undetectable level of HCV, i.e., in the absence of serum HCV-RNA, localized to the liver, although it rarely does so (22). However, her persistent HCV-PCR negativity may account for the very low possibility of HCV recurrence.

The recipient was also at risk of suffering a CMV-related vascular complication because of the CMV seromismatched transplantation. Vascular injury caused by CMV infection is well known regarding, in particular, the incidence of hepatic artery thrombosis (HAT) after OLT. The injury occurs in not only the vascular endothelium, but also the sinusoidal endothelium. In response to the infection, intercellular adhesion molecule 1 (ICAM-1), which is not detected on normal sinusoidal endothelial cells (SECs), is induced by monokines such as interleukin-1 and tumor necrosis factor 1 alpha in the sinusoidal endothelium, leading to marked disturbance of the sinusoidal microcirculation (23). Nevertheless, the early SOS in case 2 is not likely to have been associated with CMV, especially as the patient's CMV-PCR was consistently negative because of the administration of prophylactic ganciclovir.

It is noteworthy that this patient received a whole liver from a 75-yr-old woman. Pathologic study of the donor liver just prior to procurement showed 30% steatosis and centrilobular perisinusoidal fibrosis, the latter being a common finding in elderly livers. Apart from alcoholic hepatitis, these findings often originate from non-alcoholic metabolic syndrome, and correspond to this donor's long medical history of systemic hypertension and hypercholesterolemia. Because many types of insult can produce oxidative stress and toxic metabolites under these situations, the liver requires a fair amount of glutathione to detoxify these injurious stressors. However, the availability of glutathione in fatty liver mitochondria such as in this donor is evidently reduced. Consequently, abundant metabolites of drugs are seen in the hepatocytes, which have not been sufficiently detoxified, that can retain their activities. Thus, the profound glutathione depletion and rich toxic metabolites might have promoted extensive injury to the SECs in case 2. Although the SEC also has

the function of detoxification, the SEC intracellular glutathione concentrations are less than half that of hepatocytes, and the glutathione detoxification capacity of the SEC is therefore much less than that of hepatocytes (24). It is suggested that this weak glutathione detoxification capacity of the SEC predisposes and exacerbates sinusoidal injury.

Besides these precursory situations of the donor, some intra-operative and postoperative impacts on the graft may aggravate the function of the sinusoids. The SEC appears to be the principal target of cold preservation injury, at least during the early phase of reperfusion. SECs remain viable until oxygenated reperfusion, but the death and the denudation of sinusoids occur rapidly following reperfusion through apoptosis (25, 26). Oxidative stress: the increase in oxygen free radicals with reperfusion plays an important role in this sinusoidal injury. An experimental study revealed that *N*-acetylcysteine prevented glutathione depletion and attenuated sinusoidal reperfusion injury. The fact that glutathione has become an important component in the preservation medium since the University-Wisconsin (UW) solution supports this result. In case 2, the reperfusion after cold preservation of the allograft, which has already manifested profound reduced glutathione, might have intensified the sinusoidal damage.

A randomized study to investigate the difference in the histologic changes between cyclospoline A and tacrolimus with patients after OLT showed that prominent perivenular hepatocellular dropout, necrosis with sinusoidal dilatation, and red cell extravasation in Disse's spaces were seen in the tacrolimus group, even in the absence of cellular rejection, and this phenomenon targeting Zone 3 has suggested the toxic effect of tacrolimus (27). Recently, a lung transplant case complicated with SOS arising from strongly suspected tacrolimus hepatotoxicity, and a case of SOS, which appeared to be due to tacrolimus toxicity caused by an overdose, have been reported (28, 29). Experimental studies revealed that several drugs including azathioprine cause profound glutathione depletion in SECs before the onset of toxicity, leading to deterioration of drug toxicity (30). It may be that toxic metabolites of tacrolimus encouraged sinusoidal injury through similar mechanism as others. Furthermore, the sensitivity to the hepatotoxicity caused by active metabolites of tacrolimus varies in the individual patient, and increasing concentrations of these specific metabolites might account for the appearance of sinusoidal endothelial injury in case 2.

In this case, the actual cause of SOS is uncertain, although we strongly suspect that pre-existing degeneration in the donor liver was carried over to the recipient, and in addition, the long-term medicated donor liver, ischemic and reperfusion injury of the allograft, and tacrolimus toxicity might have interacted to promote the development of critical SOS.

A number of challenges in the treatment of severe SOS have been made with the advance in our understanding of the pathophysiology of disease. Platelet activation and subsequent thrombosis could play a role in early genesis, and marked elevation of plasma plasminogen activator inhibitor (PAI-1) in SCT-associated SOS has been observed in several studies (31, 32). Prostaglandin E1 and tissue plasminogen activator (tPA) with or without heparin have been therefore used as the predominant treatment agents. Although some improvement with tPA has been reported (33, 34), the use was limited because of such fatal complications as intracerebral or pulmonary hemorrhage arising from tPA toxicity.

Defibrotide (DF) is a single-stranded polydeoxyribonucleotide with antithrombotic, anti-ischemic, and thrombolytic effects, having originally been developed for the treatment of many vascular disorders. DF stimulates fibrinolysis through increasing endogenous tPA activity and decreasing PAI-1 levels. The important characteristic of this agent is the absence of anticoagulant activity, *per se*, leading to a great advantage with the absence of serious complications such as fatal hemorrhage. The application of DF for severe SOS after SCT during the past decade has achieved rather favorable results, and DF was subsequently to be used in the management of SOS after solid organ transplantation. In two case reports (two patients in each) of SOS after OLT treated with DF, only one of four had a complete response in disappearance of ascites and decrease of bilirubin levels (35, 36). One explanation for this result could be that the timing of the diagnosis of SOS, and the interval between the onset of disease and administration of DF might impact on the response to DF. In this study, DF was not attempted because of its unavailability for SOS after OLT in France. The conclusive evaluation seems to be premature because of the paucity of clinical use of DF in the liver transplantation setting. Although DF is thus not yet available worldwide for SOS after OLT, a further large, prospective study of DF for SOS in liver transplant patients will be warranted because of its promise as a therapeutic agent.

In this report, both patients underwent TIPS placement to resolve intractable ascites. TIPS as a treatment for SOS was first reported in 1996, for a patient who had received bone marrow

transplantation, and the procedure resulted in regression of hepatic and renal symptoms (37). In the liver transplantation setting, the first TIPS was performed in a patient with massive ascites associated with persistent portal hypertension of unknown origin in 1998 (38). Dramatic correction of liver dysfunction is achieved in some cases. In portal hypertension complicated with ascites, some reports have documented that TIPS is considered in cases of no or poor response for the use of a sodium restricted diet and maximal dose of diuretic treatment, or cases who fail to respond to large volume paracentesis (39, 40). However, the precise indications and optimal timing of this procedure in SOS remain to be clarified since long-term follow-up of TIPS in overall indications is scarce. In the present study, TIPS has contrasting results in our two cases: one with complete recovery both in clinical symptoms and in liver function, and the other with failure resulting in re-transplantation. The cause–effect relationship between SOS and TIPS remains unknown. Meanwhile, regarding our two cases, the differences in clinical course after onset and its attendant management until TIPS might decide the patient's fate. In case 2, the progress of the disease was deadly rapid, and she underwent no fewer than nine sessions of paracentesis during one month, being finally complicated with renal dysfunction before TIPS. The lack of benefit of TIPS in this case could be ascribed to the delayed delivery of this procedure. It must be even more important to discern the optimal timing of TIPS from the clinical aspect in the progress of SOS. We suggest an earlier attempt of TIPS when there is no response to all initial medical treatments leading to repeated large-volume paracentesis in the short term, because clinical status submitted to prolonged refractory ascites will certainly increase the risk of fatal complications in patients with an extremely compromised condition as in our case 2. It seems reasonable, as Rössel et al. reported that failure of paracentesis is defined as the inability to remove the ascitic fluid or the need for large-volume paracentesis more than once per week (41).

Senzolo et al. have described that a HVPG > 20 mmHg would benefit from TIPS (42). Although the HVPG in case 2 was not significant, the question regarding proper evaluation of the progression of sinusoidal hypertension at that time must have considerable weight. A close study on the HVPG in cirrhosis patients revealed differences in the HVPG values in different hepatic veins because of intrahepatic veno-venous communications (43). In addition to this heterogeneity of the vascular structure, these differences probably may represent a notable heterogeneity in the regional variability of fibrosis in cirrhosis (44). The HVPG in case 2 therefore might have been much higher in the other intrahepatic veins.

Little positive consideration has been given to date regarding the treatment with TIPS for severe SOS because it does not improve the outcome of disease. In the liver transplantation setting, however, some cases with not only clinical improvement but also histologic amelioration after TIPS has been reported (36, 45). In fact, our case 1 retains an excellent condition with normal liver function and no recurrence of ascites for 21 months after TIPS. Although only a few case reports of TIPS for progressive SOS after OLT have been presented, and although various challenges including the optimal timing of TIPS and the stratification of patients into the best candidate for TIPS remain to be clarified, TIPS could have a potential to become a curative modality. Further clinical trials with multiple institutes are necessary.

In conclusion, we have presented two cases of intractable ascites associated with SOS, one of them successfully treated after TIPS placement. In the event of refractory ascites after OLT, resistant to all available medical therapies, the complication of SOS must always be kept in mind. Although differentiating SOS on clinical grounds from other pathogeneses as the cause of refractory ascites is not so easy because of its relatively non-specific clinical features, it is quite important because therapeutic strategy thereafter will altogether differ depending on the cause. Contemporaneously, the diagnosis of SOS is required as early as possible, as the outcome of the disease can be considerably affected by the start of specific treatments. Further investigation for SOS after OLT should have to be continued to identify a cure without re-transplantation, because re-transplantation as a last resource undoubtedly worsens the outcome regardless of the cause of the necessity of a second allograft.

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