Graft Failure From Hepatic Veno-Occlusive Disease After a Liver Transplant: A Case Report

Tian Shen, Xiaofeng Tang, Hua Xiang, Shusen Zheng

Abstract

Objectives: Hepatic veno-occlusive disease after liver transplant is rare but potentially fatal. Here, we describe a case of veno-occlusive disease occurring after a liver transplant patient, which resulted in graft failure.

Case Report: A 44-year-old woman developed severe ascites accompanied with jaundice, for 1 month after a liver transplant that could not be explicated by common complications. Veno-occlusive disease was diagnosed basing on clinical, pathologic, and radiologic findings. The definitive pathogenesis was difficult to determine. The patient could not show any response to medical therapy, and her deteriorated clinical condition developed to hepatic failure, which called for retransplant.

Conclusions: Veno-occlusive disease after a liver transplant can result in graft failure, and re-transplant may be the only alternative resource in critical case.

Key words: Veno-occlusive disease, Liver transplant, Graft failure

Introduction

Hepatic veno-occlusive disease (VOD) is an unusual clinical syndrome characterized by hepatomegaly, abdominal pain, ascites, and jaundice, resulting from fibrotic obliteration and congestion of the hepatic centrilobular veins.1 Hepatic VOD is observed most frequently in individuals who have consumed wild herbs containing pyrrolizidine alkaloids.2 In the transplant field, patients who have undergone hemopoietic stem cell transplant, are more likely to develop hepatic VOD, because of chemoirradiation preconditioning regimens than solid-organ transplant recipients.1 In solid-organ transplant settings, VOD has been sporadically reported after kidney, liver, and lung transplants attributed to azathioprine, immunological reaction, or tacrolimus.3-7

Published cases of VOD after liver transplant are limited, with an incidence of approximately 2%.8,9 Veno-occlusive disease after liver transplant is lethal because of graft failure in some cases.10 However, the optimal treatment and prognosis of VOD after liver transplant is not well known. Here, then, we present a case of hepatic VOD as a severe complication of liver transplant, which led to graft failure. The exact cause and pathophysiological processes remain obscure.

Transplants were performed after obtaining fully informed written consent from the donor’s authorizer and recipient, and they were approved by the Liver Transplant Committee of Zhejiang University. All of the protocols conformed with the ethical guidelines of the 1975 Helsinki Declaration.

Case Report

A 44-year-old woman received a liver transplant because of autoimmune liver disease. The graft was obtained from an ABO-identical donation after cardiac death (DCD). Information of the donor was as follows (sex, male; age, 36; BMI, 22; cause of death, cerebral hernia due to traffic accident; liver function, normal. Serum markers of hepatitis virus A, B, C, D, E, and HIV, negative; warm ischemia time, 5 minutes; cold ischemia time, 9 hours). A biopsy specimen of the graft before transplant showed that it was almost normal. Intraoperative Doppler ultrasonography confirmed satisfied flow of the hepatic artery, hepatic
vein, and portal vein after reconstruction. Postoperative immunosuppressants were combinations of tacrolimus, mycophenolate mofetil, and tapering of corticosteroids. The early postoperative period was uneventful, and the patient was discharged 3 weeks after transplant with normal graft function and clinically stable condition. The follow-up examinations revealed nothing special, and the trough concentration of tacrolimus was controlled between 7 and 10 ng/mL.

But she began to present with fatigue, poor appetite, abdominal distension, and pain at 32 days after transplant. Three days later, she was hospitalized again. This time, her serum amino-transferase and aspartate aminotransferase levels increased slightly to 45 U/L and 57 U/L, accompanied with the rising serum total bilirubin concentration (31 \( \mu\)mol/L) and decreased serum albumin level (34 g/L) at that point. The trough concentration of tacrolimus was higher than 30 ng/mL, and an increasing creatinine level was seen of 156 \( \mu\)mol/L. Doppler ultrasonography image revealed massive ascites with normal flow in the hepatic artery, hepatic vein, and portal vein. Considering the high level of tacrolimus and injured renal function, we stopped using the drug. At the same time, yellowish ascites was drained out through a tube. The medicines of albumin and diuretic were performed simultaneously. The patient felt a little better by drainage of ascites, with the volume between 500 and 1000 mL/day.

On day 38, the aminotransferase level normalized to 23 U/L, the total bilirubin level was similar to that observed in a previous examination, and the patient’s tacrolimus level dropped to 21.4 ng/mL. A computed tomography (CT) scan showed large amounts of ascites, hepatic enlargement, patchy liver enhancement, and obscure hepatic veins, which were regarded as typical features of VOD (Figure 1A). Doppler ultrasonography was done again to confirm any problem of blood flow, and relatively thin hepatic vein with slow portal vein flow was found. Budd-Chiari syndrome or anastomotic stenosis of hepatic vein was excluded by angiography (Figure 1B).

According to the clinical and radiologic manifestations, we established a provisional diagnosis of VOD. Anticoagulant therapy of low-molecular weight heparin plus prostaglandin E began to be administered. Because there was no evidence of particular toxic agents consumed, tacrolimus was suspected to be the possible predisposing factor and continued to be stopped. On day 41, the level of tacrolimus was 7.6 ng/mL, and the creatinine concentration had decreased to normal. Liver function was little changed. Then, cyclosporine began to be applied as one of immunosuppressors. However, the drainage of ascites continued to increase and the symptomology of painful hepatomegaly worsened as well. Moreover, the graft function deteriorated gradually with total bilirubin level up to 151 \( \mu\)mol/L on day 52.

There were no signs of magnetic resonance cholangiopancreatography of biliary anastomotic stenosis or intrahepatic biliary dilation. The possibility of viral hepatitis or recurrence of autoimmune hepatitis was excluded. A liver specimen was obtained.

**Figure 1.** (A) Computed Tomographic (CT) Scans on Day 38 Demonstrated Ascites, Hepatic Enlargement, Patchy Liver Enhancement, and Obscure Hepatic Veins; (B) CT Angiography Demonstrated No Significant Stenosis or Occlusion in the Inferior Vena Cava and the Portal Vein (PV).
through ultrasound guidance. Veno-occlusive disease was diagnosed by the typical signs revealed by pathology: centrilobular necrosis, sinusoidal congestion, and fibrotic obliteration of centrilobular veins (Figure 2). Jaundice and coagulation continued to deteriorate (peak total bilirubin level was 414 μmol/L, prothrombin time level was 33 s, on day 72) with no response to medical therapy, and required intervention of artificial liver system for 3 times, which reduced the jaundice temporarily. Cyclosporine dosage was obviously lower than general to get at the target blood level (100-150 ng/mL). No clinical or radiologic improvement was found. She became weaker because of severe jaundice and ascites. She received liver retransplant (DCD) 3 months after the first transplant for graft failure. The explant was characterized by congestive and swelling liver, and stenosis of inferior vena cava (IVC) or large hepatic vein was excluded (Figure 3). After the second transplant, she has remained asymptomatic for 8 months.

**Details on donors**

**Donor 1 (first transplant):** A 36-year-old man went through a motor vehicle accident and had severe craniocerebral trauma, which finally developed to cerebral hernia. No intensive medical or surgical therapy showed an effect. After assessment by the Organ Procurement Organization (OPO), he was considered to be a potential donor. Then, the OPO obtained full-informed consent from the donor’s authorizers. After the patient was declared dead (brain death to cardiac death), the OPO obtained liver and kidneys from the donor. (Gender, male; age, 36; weight, 67 kg; BMI, 22; cause of death, cerebral hernia and cardiopulmonary arrest; serum alanine aminotransferase, 51 U/L; serum total bilirubin, 15 μmol/L; serum prothrombin time, 11 s; serum creatinine, 67 μmol/L; serum sodium, 148 μmol/L; white blood cell count, 13 × 10⁹/L; platelet count, 252 × 10⁹/L; hemoglobin, 125 g/L; Serum markers of hepatitis A, B, C, D, E, and HIV all were negative; warm ischemia time, 5 minutes; cold ischemia time, 9 hours.)

**Donor 2 (retransplant):** A 45-year-old man had a cerebral hemorrhage after rupture of vascular malformation. No intensive medical or surgical therapy proved effective. After assessment by the Organ Procurement Organization (OPO), he was considered to be a potential donor. Then the OPO obtained fully informed consent from the donor’s authorizers. After the patient was declared brain dead, the OPO obtained the liver and the kidneys from the donor. (Gender, male; age, 45; weight, 69 kg; BMI, 23; cause of death, cerebral hemorrhage after
rupture of vascular malformation; serum alanine aminotransferase, 32 U/L; serum total bilirubin, 10 μmol/L; serum prothrombin time, 12 s; serum creatinine, 79 μmol/L; serum sodium, 145 μmol/L; white blood cell count, 11 × 10⁹/L; platelet count, 193 × 10⁹/L; hemoglobin, 132 g/L; serum markers of hepatitis A, B, C, D, E, and HIV were negative; warm ischemia time, 6 minutes; cold ischemia time, 7 hours.)

Discussion

Veno-occlusive disease after liver transplant is rare but is potentially fatal because of graft dysfunction. Several cases with VOD after liver transplant have been reported, involving cases of deceased-donor and living-related, adult and pediatric recipients. Two review articles of large series mentioned that about 1.9% to 2.3% of patients after deceased donor’s liver transplant had VOD at various times after transplant.

The clinical symptoms related to VOD are nonspecific, which induces the fact that diagnosing of VOD in postliver transplant patients is more difficult and confused than that which occurs in other types of transplants. Jaundice after liver transplant is common and attributed to a wide range of reasons; including biliary complications, recurrence of viral or auto immunologic hepatitis, rejection, ischemic injury, and drug toxicity. Refractory massive ascites after liver transplant is often related to outflow disturbance such as anastomotic stenosis of hepatic vein and chylous leakage. Therefore, VOD can be hardly distinguished from other common complications of liver transplant only relying on clinical manifestations.

According to our knowledge, VOD is triggered by damage to endothelial cells of the hepatic venules and sinusoids, which results in centrilobular necrosis and progressive centrifugal fibrotic obliteration. Then, reduced hepatic venous outflow leads to portal hypertension and hepatic injury.

The radiologic features also can play important roles in diagnosing VOD after a liver transplant. Ascites, usually accompanied with pleural effusion, patchy liver enhancement, and narrowing of main hepatic veins are considered to be the first presentations in CT and magnetic resonance imaging. Because venous outflow obstruction (eg, Budd-Chiari syndrome and anastomotic stenosis of hepatic vein) remains to be a major differential diagnosis, radiologic judgment of the inferior vena cava and the hepatic venous anastomosis are important.

So, there can be considerable overlap in the clinical and histologic characteristics seen in VOD across series of disorders that may occur in liver allografts. It is recommended that diagnosing VOD after liver transplant be based on established clinical criteria, combined with pathologic findings and radiologic presentations.

The case described here presented with symptoms of severe ascites, followed by aggravating jaundice. Common complications after liver transplant (eg, acute rejection, hepatitis, bile duct compromise, and outflow obstruction) were excluded by pathologic and radiologic investigations. Interestingly, the patient showed extremely sustained high level of tacrolimus despite its discontinuation. It could be explained by the fact that pathophysiologic process of VOD affects in this working.

This is tacrolimus metabolism and drug elimination is delayed, as well as cyclosporine. Similar phenomena were observed in hemopoietic stem cell transplant patient who had VOD. It suggests that calcineurin inhibitor-induced toxicity should be taken into account in liver transplant recipients with VOD.

Compared with diagnosis, the cause of the disease in the present case was uncertain. In the past, occurrence of VOD after liver transplant most often was related to azathioprine treatment. According to a report from 1994, forty-three percent of the patients after undergoing a liver transplant developed hepatic VOD with azathioprine. For this reason, azathioprine has been replaced by new immunosuppressants worldwide, report of VOD associated with this agent currently is rare. It should be emphasized that recent researches tended to support the hypothesis that immunologic responses may participate in the onset of VOD after liver transplant (including acute cellular and humoral rejection). Tacrolimus might be another possible agent to induce VOD because it precipitates dysregulation of endothelial cells. But the cases of VOD presumably associated with tacrolimus, are even rarer than azathioprine and immunologic phenomenon.

The patient described here had never been exposed to any cytotoxic agents such as azathioprine...
or particular herbs before and after transplant. And the evidence of acute rejection was absent, not only in clinical manifestations, but also in biopsy specimens. Therefore, we assumed that tacrolimus was most likely the predisposing agent at the beginning of progression. Unfortunately, the patient’s symptoms could not be resolved after discontinuation of tacrolimus. In fact, the exact pathogenesis of VOD remains obscure in this patient.

Successful treatment of VOD is usually directed to the underlying cause. Withdrawal of offending drugs is effective. In part of cases associated with rejection, intensive immunosuppressive treatment or intervention of antibody-mediated rejection might play role although no standard has been established.7,9 Efficiency of anticoagulant therapy and improving microcirculation is unclear. Transjugular intrahepatic portosystemic stent-shunt has been proven to be helpful in clinical improvement of ascites but has no effect on jaundice and survival.9,15 Mortality is unclear because of the limited cases. In general, the prognosis of VOD after a liver transplant varies from complete resolution after withdrawal of the predisposing agents, to a fatal outcome resulting from hepatic failure. Re-transplant should be performed as salvage therapy when graft failure developed.

In conclusion, we diagnosed an unusual case of VOD after a liver transplant. Determination of the cause and pathogenesis of VOD in this patient was difficult. Re-transplant may be the only alternative resource in critical case with graft failure. Enhanced understanding of the mechanism underlying this disease is warranted.

References