ELSEVIER

Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome Associated With Potential Antibody-Mediated Rejection After Pediatric Living Donor Liver Transplantation: A Case Report

N. Yamada, T. Urahashi, Y. Ihara, Y. Sanada, T. Wakiya, N. Okada, and K. Mizuta

ABSTRACT

A 9-month-old girl with biliary atresia underwent successful living donor liver transplantation from her 42-year-old ABO blood-type incompatible mother. The postoperative course was uneventful until postoperative day (POD) 13 when the recipient displayed an increased volume of drained ascites and decreased her platelet count showing low-velocity portal venous inflow without hepatic venous outflow obstruction. We suspected potential veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) due to an acute cellular rejection (ACR) episode and performed a liver biopsy (LB). We diagnosed severe episode (Rejection Activity Index Score; P3V3B1 = 7) and started steroid pulse therapy. We performed a second LB on POD 27 because the patient showed weight gain and tender hepatomegaly, diagnosing moderate ACR (P1V3B1 = 5). We started a second course of steroid pulse therapy, but the patient's clinical findings did not improve. On POD 43, her third LB finding showed P1V1B1 with improved processes from ACR, but still displaying severe congestion and fibrotic obliteration of small hepatic veins. We suspected that her immunologic responses were associated with antibody-mediated rejection (AMR) because her anti-HLA class I and class II antibodies were positive by flow panel-reactive antibody method and donor-specific antigen class II and C4d staining were also positive. We added mycophenolate mofetil and administered high-dose intravenous immunoglobulin to control the AMR, and anticoagulant therapy for the VOD/SOS. Her clinical findings and graft venous abnormalities finally improved; she was eventually discharged without sequelae on POD 72.

VENO-OCCLUSIVE DISEASE/SINUSOIDAL OBSTRUCTION SYNDROME (VOD/SOS) is characterized by hepatomegaly, ascites, weight gain, and jaundice.[1–3] Most cases of VOD/SOS in the transplantation field have been reported after preconditioning treatments for bone marrow transplantation, or immunosuppression associated with renal transplantation.[4,5] In liver transplantation (OLT), VOD/SOS is a rare cause of graft dysfunction, considered to be the result of sinusoidal endothelial cell damage in the centrilobular zone (zone 3).[6] Some cytotoxic drugs and/or immunologic responses may be associated with this entity, but the causes and pathophysiological processes of VOD/SOS after OLT are not well known.[7,8] We have herein reported a case of VOD/SOS after pediatric living donor liver transplantation (LDLT) associated with potential antibody-mediated rejection (AMR).

CASE REPORT

A 9-month-old girl (body weight 8.2 kg) with biliary atresia after undergoing a Kasai portoenterostomy was referred to our hospital for LDLT. She was not found to have ascites or a pleural effusion. A lymphocytotoxic crossmatch test (LCT) using a direct complement-dependent cytotoxicity assay was negative. As no suitable voluntary living ABO-compatible donor was available, she underwent successful LDLT from her 42-year-old ABO blood-type incompatible mother. The graft volume (GV) was 235 g and graft volume per standard liver volume, 89.0%. The operation was uneventful. We used tacrolimus and methylprednisolone for post-

From the Department of Transplant Surgery, Jichi, Medical University, Tochigi, Japan.

Address reprint requests to Naoya Yamada, MD, Department of Transplant Surgery, Jichi Medical University, 3311-1 Yakushiji, Szhimotsuke-shi, Tochigi, 329-0498 Japan. E-mail: yn708@jichi.ac.jp

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operative immunosuppression. The patient's clinical course, shown in Fig 1, was uneventful until postoperative day (POD) 13 when there was an increased volume of ascites (>300 mL/d), a decreased platelet count, and development of low-velocity portal venous inflow without hepatic venous outflow obstruction. Although her serum hepatic transaminase levels were almost normal, we suspected potential VOD/SOS and thus performed a liver biopsy (LB). Initially, we diagnosed a severe acute cellular rejection episode (ACR; Rejection Activity Index Score [RAIS]: P3V3B1 = 7; Fig 2 A) and started steroid pulse therapy. However, the patient demonstrated weight gain with tender hepatomegaly (GV; 505 mL) and splenomegaly (143 mL). On Doppler ultrasonography, she displayed high-velocity hepatic venous outflow and decreased pulsatile hepatic venous wave forms. We performed a second LB on POD 27 that showed cellular infirtration especially around the central vein (zone 3; Fig 2 B1). C4d staining was also positive at that time especially around the portal areas (Fig 2 B2). We diagnosed moderate ACR (RAIS; P1V3B1 = 5), considering that her condition could be explained as VOD/SOS followed by ACR, and initiated a second course of steroid pulse therapy. Despite trying to control her immunologic responses, the patient's clinical findings and graft inflow/outflow abnormalities did not substantially improve. On POD 43, her third LB finding showed P1V1B1 with improved processes from ACR, but still with severe congestion and fibrous obliteration of small hepatic veins (Fig 2C). Although her anti-ABO antibody values were normal, we suspected antibody-mediated rejection (AMR), because her anti-HLA class I and II antibodies were positive by the flow panel-reactive antibody method (flow PRA) as well as positive donor-specific antigen class II and C4d staining time. We added mycophenolate mofetil (MMF) and administered high-dose intravenous immunoglobulin (IVIG) to control the AMR for 5 days and anticoagulant therapy for the VOD/SOS. After these treatments, her clinical findings of hepatosplenomegly as well as graft inflow/outflow abnormalities finally improved. On POD 61, her fourth LB showed improved congestion and fatty changes without cellular infiltration (Fig 2D). She was eventually discharged without sequelae on POD 72.

DISCUSSION

Although the condition was first described in 1950s by Bras et al,[9] the pathogenesis of hepatic VOD/SOS still remains unclear. In the transplantation field, most cases of VOD/SOS have been reported after preconditioning treatment for bone marrow, or immunosuppression associated with renal grafting.[4] In OLT, VOD/SOS is rare, but it includes a risk for early graft failure.[10] A previous study indicated that about 1.9% of patients who underwent deceased donor OLT suffer VOD/SOS at various times after transplantation.[11] The patients with VOD/SOS typically show clinical symptoms such as tender hepatomegaly, fluid retention, and jaundice. These findings closely resemble those of hepatic venous outflow obstruction despite the lack of mechanical

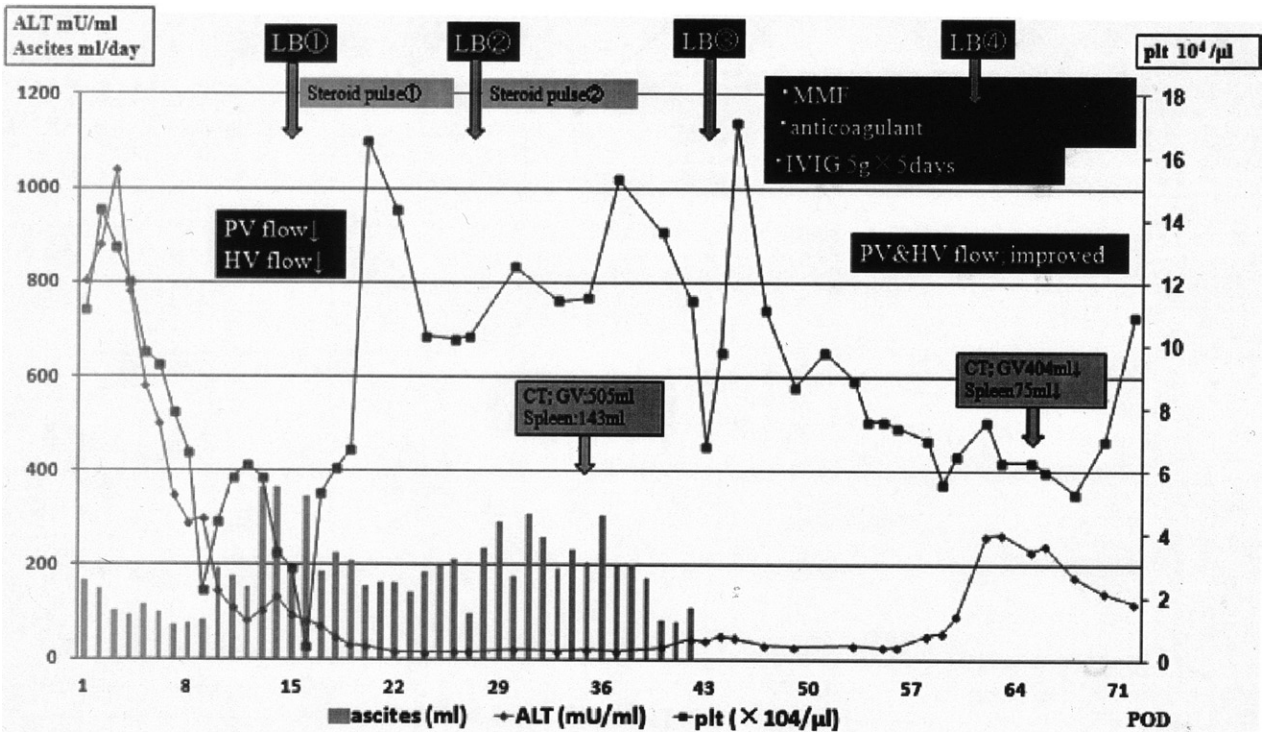

Fig 1. The clinical course of the patient after living donor liver transplantation. We performed a liver biopsy (LB) on postoperative day (POD) 13, 27, and 43. Despite a second course of steroid pulse therapy, her clinical findings did no improve. We added mycophenolate mofetil (MMF) and intravenous immunoglobulin (IVIG) to control the antibody-mediated rejection, and anticoagulant therapy for the veno-occlusive disease/sinusoidal obstruction syndrome. After these treatments, her clinical findings (hepatosplenomegly as well as graft inflow and outflow abnormalities) improved. LV, liver biopsy; ALT, alanine aminotransferase; PV, portal venous inflow; HV, hepatic venous outflow; CT, computed tomograhy; GV, graft volume.