Abstract

Antibody-mediated rejection after liver transplant, especially when the donor is not a direct relative; it is associated with additional inconvenience for patients. We encountered a case in which antibody-mediated rejection because of de novo donor specific antibodies against donor human leukocyte antigen developed 6 months after ABO-compatible living-donor liver transplant and was treated with retransplant. A 38-year-old man with hepatitis B virus-related hepatocellular carcinoma underwent living-donor liver transplant with a graft from his wife. Six months later, he experienced fatigue and jaundice. Liver biopsy revealed C4d deposits, and histologic examination showed an antibody-mediated rejection pattern. We re-evaluated recipient-donor human leukocyte antigen matching and tested the patient’s blood for antihuman leukocyte antigen donor-specific antibodies against donor human leukocyte antigen. De novo auto antibodies against human leukocyte antigen-DQ6 were identified by Luminex single antigen beads. Because exhausting all treatment options, a rescue second living-donor liver transplant was planned with the patient’s stepdaughter as the donor. Pretransplant human leukocyte antigen matching was performed with the patient’s stepdaughter as the donor. Pretransplant human leukocyte antigen matching was performed, and the patient was discharged without event. Two months later, hyperbilirubinemia was noted, and a residual common bile duct from the first donor with chronic fibrosis and stricture was strongly suspected. Redo hepaticojejunostomy was successfully performed, with no problems during 1-years’ follow-up. Thus, liver retransplant could be a rescue treatment for antibody-mediated rejection complicated with hepatic failure.

Key words: ABO-compatible, Antibody-mediated rejection is caused by the presence of autoantibodies to human leukocyte antigens (HLAs), Allograft failure, Autoantibodies, Liver retransplant.

Introduction

Antibody-mediated rejection after liver transplant is an important cause of allograft injury or loss. Antibody-mediated rejection is often difficult to diagnose because its symptoms are nonspecific, there are no standardized diagnostic techniques, and its mechanism is unclear. Antibody-mediated rejection rarely develops in cases of ABO-compatible liver allograft, as it is relatively resistant compared with other solid-organ transplants. The therapeutic approaches for antibody-mediated rejection include intravenous immunoglobulin, plasmapheresis, altered maintenance immunosuppression alone, or a combination of these. However, the therapeutic effect remains controversial, and patients still have allograft dysfunction or failure.

In this report, we present a patient who underwent ABO-compatible living donor liver transplant with a graft from his current wife. Liver allograft injury because of ABO-compatible living-donor liver transplant-related antibody-mediated rejection was treated with retransplant. We report the details of this case here with a review of the literature.

Case Report

A 38-year-old man with hepatitis B virus-related hepatocellular carcinoma, T2N0M0, and stage II, underwent surgical intervention and received locoregional therapy for recurrence repeatedly between April 2012 and February 2013. In May 2013,
he underwent ABO-compatible LDLT per the University of California San Francisco criteria. A right lobe graft, 535 g, was donated by his current wife. After the operation, liver allograft function was good under control with immunosuppressants. The patient was discharged without complications after hospitalization for 10 days and received regular outpatient follow-up. About 6 months later, intermittent cholangitis and severe jaundice were noted. Initially, an after liver transplant biliary anastomosis stricture was suspected after evaluation by endoscopic retrograde cholangiopancreatography endoscopic retrograde cholangiopancreatography (Figure 1A). However, no obvious dilatation of the intrahepatic biliary tree was noted. Magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography were performed multiple times and biliary stent implantation was attempted but failed. Eventually, percutaneous transhepatic catheter drainage of the biliary tree was performed (Figure 1B). The average amount of daily bile drainage was about 100 mL, and severe jaundice persisted. In addition, ischemic cholangiopathy was suspected. Doppler sonography and computed tomography angiography of the liver vessels revealed a patent hepatic graft artery (Figure 1C). Hyperbilirubinemia persisted, and the patient suddenly developed coma in consciousness in July 2014. Based on the clinical presentation and evaluation of liver function, allograft failure, related to hepatic encephalopathy was strongly suspected and confirmed by liver biopsy, which revealed mononuclear cell infiltration, massive hepatocyte necrosis, arteriopathy of hepatic artery, prominent bile duct damage, and C4d deposits. Antibody-mediated rejection was strongly suspected on the basis of the clinical symptoms and histologic examination findings (Figure 2). Repeated plasmapheresis and anti-CD20 therapy were prescribed, but the therapeutic effect was poor. Simultaneously, recipient-donor HLA matching was re-evaluated, and DSAs against HLA class II, which were de novo DQ6 autoantibodies, were detected by Luminex single antigen beads (mean fluorescence intensity value: 9645, cut-off value: 1500) with positive flow-cytometric crossmatches in the patient’s serum.

The autoantibodies attacked the allograft, resulting in allograft dysfunction and even loss. Consequently, after exhausting all treatment options and discussing the issue with the patient’s family, liver retransplant was planned. Based on favorable recipient-donor HLA matching (Table 1), the right lobe graft was obtained from the patient’s stepdaughter. The operation was performed in August 2014. Grossly, atrophic changes were noted in the first allograft, and a marked cholestasis pattern was observed. The common bile duct was preserved.

![Figure 1](image.png)

**Figure 1. Assessment of Biliary Tract After Liver Transplant When Unreasonable Hyperbilirubinemia Developed**

(A) Endoscopic retrograde cholangiopancreatography showing a suspected postliver transplant biliary anastomosis stricture without intrahepatic bile duct dilatation.

(B) Percutaneous transhepatic catheter drainage for bile drainage (only a small amount of bile juice was drained).

(C) Computed tomography angiography showing a patent hepatic graft artery with ischemic cholangiopathy seeming less likely.

| Table 1. Mean Times Required To Perform Each Portion of the Procedure |
|--------------------------|-------------------|-------------------|
| **Recipient**            | 1st Donor         | 2nd Donor         |
| **Gender**               | M                 | F                 | F                 |
| **Blood type**           | AB+               | O+                | A+                |
| **HLA-ABC**              | A2, A33           | A2, A11           | A11, A33          |
|                          | B60, Bw6          | B27, B51, Bw4     | B48, B60, Bw6     |
|                          | Cw10, Cw15        | Cw12, Cw14        | Cw8, Cw10         |
| **HLA-DR**               | DR8, DR12,       | DR15, DR17,       | DR4, DR8,         |
|                          | DR52              | DR51, DR52        | DR53              |
| **HLA-DQ**               | DQ4, DQ7          | DQ2, DQ6          | DQ4, -            |
| **Kinship**              | Current wife      | Stepdaughter      |

Results are means ± standard deviation.
because of difficulty in the surgical approach and dense adhesion of the hepatic hilum. Biliary reconstruction using duct-to-duct hepaticocholedochostomy was performed.

Antibody-mediated rejection–related hemorrhagic infarction was confirmed by final histologic examination. The patient recovered and was discharged without complications after being hospitalized for 11 days. However, hyperbilirubinemia developed 2 months later, and chronic fibrosis and stricture of the residual common bile duct was strongly suspected based on MRCP findings (Figure 3). Redo hepaticojejunostomy via the choledochoscopic light-guided method was successfully performed. The patient has been followed for 1 year without any adverse events.

Discussion

We present what is to our knowledge the first case of liver retransplant for the management of ABO-compatible LDLT-related antibody-mediated rejection. This decision proved to be life-saving for a patient with allograft failure due to de novo autoantibody-related antibody-mediated rejection.

Antibody-mediated rejection is an important cause of allograft injury in cases of ABO-incompatible liver transplant. However, it rarely develops in cases of ABO-compatible liver transplant, which is relatively resistant. Antibody-mediated rejection often manifests as ischemic biliary problems, including ductopenia. Its features are similar to those of ischemia perfusion injury-related biliary complications, cellular rejection, or posttransplant virus infection. The similar symptoms make the diagnosis difficult and can result in allograft injury or loss. At the World Transplant Congress in 2014, the role of DSAs was reported to be underestimated because of the relative resistance of the liver to DSAs, the lack of DSA testing techniques, and the varied different

Figure 2. The Allograft Biopsy Showed Features Suggestive of Antibody-Mediated Rejection, Including

2a 2c 2b 2d 2e 2f

(A) portal mononuclear inflammatory cell infiltrates associated with ductular reaction and periportal interface hepatitis (H&E ×200), (B) subsinusoidal and perivenular fibrosis (H&E ×40), (C) centrilobular cholestasis and marked hepatocellular swelling (H&E ×100), (D) focally portal and periportal hemorrhagic necrosis (H&E ×100), (E) C4d immunofluorescent stain showing sinusoidal deposition (×400), and (F) C4d immunoreactivity observed in endothelium of portal veins and arteries (×400).

Figure 3. The Segment “B1” is the Recipient’s Original Common Bile Duct (Segment B1).

Abbreviations: A, hepatic artery; IVC, inferior vena cava; P, portal vein; Segment “B2” is the residual common bile duct from the first donor (segment B2). Thickened wall and severe stricture are noted.
phenotypes of outcomes. Accordingly, antibody-mediated rejection should be considered in the differential diagnosis of liver allograft dysfunction or unexplainable biliary complications.

The diagnostic criteria for antibody-mediated rejection for kidney or heart transplants include clinical evidence of graft dysfunction, histologic evidence of tissue injury, immunopathologic evidence of antibody-mediated rejection (ie, C4d deposits), and serologic evidence of DSAs, or other antidonor antibodies. In recent decades, a series of studies and observations on the detection, monitoring, and treatment of antibody-mediated rejection in cases of solid-organ transplants has been published. These studies recommend DSA testing, monitoring of de novo DSA development, and adequately treating antibody-mediated rejection if required as the current strategy for solid-organ transplants to preserve allograft function.

In contrast to renal transplants where DSAs are known to cause allograft failure, the effect of DSAs on liver allografts has not been clearly established. Most previous studies have focused on performed DSA, which could result in a higher risk of acute rejection or allograft injury. In addition, several recent studies have demonstrated the association of de novo DSAs after transplant with chronic rejection or allograft failure. Kaneku and associates reported that about 8.1% of patients developed de novo DSAs 1 year after liver transplant and that about 14.8% of patients with de novo DSAs 1 year after transplant died because of a nonfunctioning allograft. In that study, 95% of de novo DSAs were against HLA class II antigens, especially against the DQ antigen, similar to the case in renal transplant. Recent studies have indicated that DSA production is a result of an ongoing inflammatory reaction in the allograft, such as an infection or episodes of rejection or inflammation because of the operation. However, DSAs not only cause rejection, but also unreasonable biliary complications and allograft fibrosis. These further inconvenience patients with antibody-mediated rejection as repeated hospitalization is required, and the patients experience progressive decompensated liver dysfunction.

Based on the management strategies for renal transplant-related antibody-mediated rejection, multiple therapeutic approaches have been used for liver transplant-related antibody-mediated rejection, including intravenous immunoglobulin, plasmapheresis, antilymphocyte antibodies, immunoadsorption, altered maintenance immunosuppression alone, or a combination of these modalities. Several agents and interventions to enhance the effect of these modalities are also available, such as splenectomy, anti-CD20 antibodies, and bortezomib. The principle of antibody-mediated rejection treatment is the elimination and monitoring of circulating DSAs, inhibition of B-cell progression to plasma cells, depletion of plasma cells, suppression of the cell cycle, and proliferation of both B and T cells. However, the therapeutic effectiveness remains inconsistent and controversial.

In the present case, the non-specific symptoms confused the transplant physicians. The final diagnosis was made 8 months after rejection occurred. All recommended attempts to eliminate the circulating DSAs failed, and liver allograft loss-related decompensated end-stage liver disease developed. No studies have reported on rescue treatment for antibody-mediated rejection related to allograft failure. We performed liver retransplant after the DSAs were identified and meticulous recipient-donor HLA matching was performed. The patient recovered without adverse events, with normal liver function, and no newly developed DSAs have been detected during follow-up.

Of note, removing a failed allograft with the entire common bile duct is important. Biliary reconstruction using duct-to-duct hepaticocholedochostomy was performed in our case because of the difficulty in surgical approach and severe adhesion of the hepatic hilum during the second LDLT. We believe that the de novo DSAs continuously attacked the residual common bile duct, resulting in chronic fibrosis and even stricture. Therefore, routine Roux-en-Y hepaticojejunostomy is recommended if the residual common bile duct cannot be excised completely. This would help avoid an unnecessary operation.

In the study by Kaneku and associates, about 67.2% of postliver transplant patients with de novo DSAs survived for 1 year. However, in another study, HLA antibody-related chronic rejection resulted in progressive allograft injury and eventual loss several years later. Unless DSAs are eliminated completely with the current therapeutic modalities, post-transplant allograft failure could develop several years later. Furthermore, other non-HLA antibodies such as anti-AT1R antibody and anti-collagen V antibody had been found. All of these could cause
allograft injury or even loss. However, the mechanisms underlying these events must be established. Therefore, liver retransplant could be considered as a rescue treatment for patients with post-liver transplant antibody-mediated rejection-related allograft failure if precise identification of the autoantibody and selection of a donor such that evading these autoantibodies are possible.

References