Acute Antibody-Mediated Rejection as Cause of Late Liver Allograft Failure: A Case Report

G. Vellalta[a], C. Dopazo[a,*], I. Bilbao[a], L. Castells[b], G. Sapisochin[a], J.L. Lázaro[a], Á. Montero[c], M.T. Salcedo[c], M. Caralt[a], and R. Charco[a]

[a]Department of Hepatopancreatobiliary Surgery and Transplants, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain; [b]Hepatology Unit, Department of Internal Medicine, Hospital Universitari Vall d'Hebron, Centro de Investigación Biomédica en Red en el Área Temática de Enfermedades Hepáticas y Digestivas[CIBERehd], Universitat Autònoma de Barcelona, Barcelona, Spain; and [c]Pathology Department, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain

ABSTRACT

Background. Despite now being an infrequent complication in liver transplantation (LT) recipients, acute liver failure is still associated with high mortality.

Case Report. Here we report a case of acute liver failure 11 months after AB0-compatible LT in a hepatitis C–positive 50-year-old male recipient caused by late antibody-mediated rejection (AMR). De novo donor-specific antibodies appeared later in a previously negative donor-recipient crossmatch, leading to a rapid deterioration of liver function.

Conclusions. We highlight the importance of an accurate diagnosis and an early therapeutic intervention. The analysis of this case brings novel and generalizable insights to the differential diagnosis of acute liver failure after LT.

With the improvement in surgical techniques, perioperative management, and immunosuppression protocol, late acute liver failure after liver transplantation (LT) is becoming infrequent. Nevertheless, when liver failure does occur, technical complications or immunologic complications, among others, should be considered as the primary cause in the differential diagnosis [1,2].

Antibody-mediated rejection (AMR) is a challenging complication of solid organ transplantation, is well established in kidney or pancreas transplantation, and is frequently treatment resistant, leading to graft loss [3]. However, knowledge about acute AMR in LT is lacking. Recently, a consensus on the following criteria for diagnosis of acute AMR in liver allograft recipients was reported [3]: 1) presence of HLA donor-specific antibodies (DSA); 2) histopathologic evidence of diffuse microvascular endothelial cell injury and microvasculitis; 3) strong and diffuse C4d positivity in tissue; and 4) reasonable exclusion of other causes of liver injury. AMR occurs commonly during the early stages after transplantation in patients with preformed persistent DSA. Nevertheless, de novo DSA within the 1st year has been reported in patients without preformed DSAs at the time of LT [4,5], suggesting that de novo DSA may play a role in acute and chronic rejection, and thus in patient and graft survival.

A case of acute AMR causing liver allograft failure 11 months after LT is reported here.

CASE REPORT

A 50-year-old man was diagnosed with liver cirrhosis (Child A) due to hepatitis C virus (HCV) genotype 1b and portal hypertension with a single hepatocarcinoma nodule 3.1 cm in diameter. Pre-transplantation panel-reactive antibody was negative. After 83 days on the waiting list, he was transplanted with the liver of a 30-year-old white male donor who died from severe cranioencephalic trauma. HCV antibody test was negative. Pre-transplantation crossmatch according to flow cytometry was negative. No problems arose during surgery, which required the transfusion of 3 U red blood cells, 1 U fresh frozen plasma, and 5 pools of platelets. Cold and warm ischemia times were 250 and 50 minutes, respectively. Post-transplantation immunosuppression

*Address correspondence to C. Dopazo, Hospital Universitari Vall Hebron, Department of HBP Surgery and Transplants, Pg Vall Hebron 119-129, Barcelona 08035, Spain. E-mail: cdopazo@vhebron.net

0041-1345/15
http://dx.doi.org/10.1016/j.transproceed.2015.10.036

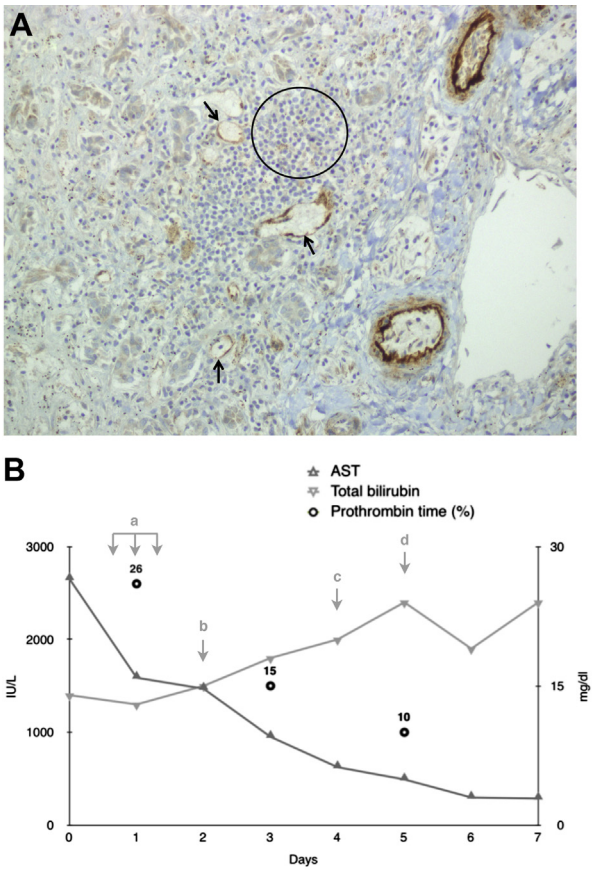

Fig 1. (**A**) Expanded portal tract with severe and polymorph inflammatory cell infiltrate (*circle*), as shown by C4d immunostaining. The staining indicates positive deposition in the arteriolar endothelium and, to a lesser extent, in the portal capillaries (*arrows*). (**B**) Liver function evolution after symptoms started (day 0). Despite the administration of 3 boluses of steroids (*a*), 2 doses of thymoglobulin (*b, c*), and plasmapheresis treatments (*d*), a steady increase of total bilirubin concomitant with a decrease in prothrombin time was observed. Abbreviations: AST, aspartate transaminase.

included 0.1 mg kg^{-1} d^{-1} tacrolimus (TAC) and 1 g/12 h mycophenolate mofetil (MMF), without steroids.

Two months after transplantation, the patient presented with liver dysfunction (aspartate transaminase [AST], 171 IU/L; alanine transaminase [ALT], 352 IU/L; total bilirubin, 0.4 mg/dL). Liver biopsy revealed mild lymphocyte cell infiltrate of portal tract and periportal endothelitis compatible with lobular hepatitis, probable recurrence of hepatitis C and suspicion of mild acute cellular rejection (Banff score, 2/1/1). HCV-RNA viral load was 5.5×10^7 IU/mL (Cobas Ampliprep/Cobas TaqMan; Roche Molecular Diagnostics, Barcelona, Spain). Impairment in renal function was observed (estimated glomerular filtration rate according to the Modification of Diet in Renal Disease 4 formula = 43 mL/min^{-1}/1.73 m^{-2}) at that time, so TAC dose was reduced with a trough level of 4–6 ng/mL maintained; MMF was reduced to 0.5 g/12 h, and everolimus (EVR) was introduced as a 3rd drug with a trough level of 3–6 ng/mL maintained.

Liver function remained stable, but owing to worsening liver function (AST, 636 IU/L; ALT, 416 IU/L; total bilirubin, 2.4 mg/dL, prothrombin time [PT] 89%) 9 months after transplantation, a new liver biopsy showed necroinflammatory lesions, including periportal necrosis and lobular necrosis graded moderate, and enlarged portal tract with septa compatible with chronic hepatitis fibrosis stage 1 according to the ISHAK score. No changes in viral load were observed. We considered reducing TAC doses to maintain a trough level of 4 ng/mL, with no changes in MMF doses, and EVR was stopped. After these adjustments in the immunosuppression therapy, a slight improvement was observed in liver function (AST, 303 IU/L; ALT, 263 IU/L; total bilirubin, 1.9 mg/dL; PT, 100%).

Eleven months after LT, the patient was admitted owing to malaise and jaundice. Blood tests showed AST of 2,508 IU/L, ALT of 2,651 IU/L, total bilirubin of 14 mg/dL, and PT of 28%, with a TAC trough level of 3.2 ng/dL. Doppler ultrasound confirmed hepatic artery and portal vein patency with no biliary tree dilatation. Screening for viral infection (cytomegalovirus, Epstein-Barr, herpes simplex, hepatitis A, B, and E) and autoimmune disease was negative. Liver biopsy revealed increased periportal fibrosis compared with the previous one, but significant signs of expansion of the portal tracts with an intense plasma cell infiltrate bile duct injury and diffuse C4d staining in arterial elastic lamina (Fig 1A) were observed, compatible with acute AMR. Immunohistochemical staining was performed on 5-μm deparaffinized and rehydrated sections of formaldehyde-fixed renal tissue, with the use of C4d rabbit polyclonal antibody (Cell Marque; Roche) in the appropriate antibody dilution (prediluted, 1:50–1:200). To block nonspecific staining, antigen recovery was performed after slide treatment by means of pressure cooking (36 minutes at 1 bar, 10 mmol/L citrate buffer, pH 9). The detection system used was Ventana (Bench Mark Ultra). Control tissue included acute antibody-mediated rejected kidneys. Luminex (One Lambda, Canoga Park, California) single-antigen assay was used for testing DSAs. The result was positive for 1 HLA class II DSA (anti-DRB1*04), and mean fluorescence intensity (MFI), which was negative at the time of the LT, was 6,800. AMR was suspected in the absence of other causes of liver failure; therefore 3 boluses of steroids (500 mg intravenously) and 2 doses of thymoglobulin (1 mg/kg) were administered, plus increased doses of TAC, without significant improvement in liver function (Fig 1B). The patient received 1 session of plasmapheresis. Meanwhile, the decision for retransplantation was made owing to the rapid deterioration course. Unfortunately, the patient died 8 days after the symptoms started, owing to intracranial bleeding with a nonfunctioning graft. Necropsy was not consented to. No C4d staining was observed retrospectively in earlier liver biopsies.

DISCUSSION

The incidence of acute AMR in liver transplantation is very low in the AB0-compatible group with a pre-transplantation crossmatch. Usually, this antibody-mediated inflammatory response and the complement appear during the early days after transplantation [6–9] in patients with persistent preformed DSA in whom liver biopsy shows microvascular injury and other characteristics typical in allograft rejection. This occurs in ~1% of all early liver allograft failure, which can reach 10% in patients with preformed DSA [10]. The incidence of de novo DSA within the 1st year after LT is 8% and it has been reported that they significantly affect patient and graft survival rates at 1 year mainly owing to their