Case Report

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Simultaneous ABO-incompatible living-donor liver transplantation and splenectomy without plasma exchange in China: Two case reports

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Abstract

ABO-incompatible (ABO-i) living-donor liver transplantation (LDLT) is performed if an ABO-compatible graft cannot be obtained. However, a perfect desensitization protocol has not been established worldwide, especially for simultaneous ABO-i LDLT and splenectomy. We herein report two cases of ABO-i LDLT. To the best of our knowledge, this is the first case report of ABO-i LDLT in an adult patient in China. Splenectomy and T-cell-targeted immunosuppression (basiliximab) was used to overcome the blood group barrier in these recipients. The patients had good graft function without signs of antibody-mediated rejection throughout the 12-month follow-up. Thus, ABO-i LDLT with splenectomy is undoubtedly life-saving when an ABO-compatible graft cannot be obtained for patients in critical condition.

Keywords

ABO-incompatible transplantation, living-donor transplantation, liver transplantation, splenectomy, treatment

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Introduction

Because of organ shortages, ABO-incompatible (ABO-i) transplantation has been performed since 1985. However, ABO-i transplantation is associated with a high risk of antibody-mediated rejection (AMR), leading to unsatisfactory outcomes for recipients. In recent years, the use of various strategies including plasma exchange, local infusion therapy, rituximab, and splenectomy have improved the outcomes of recipients of ABO-i transplantation from deceased or living donors. Although ABO-i living-donor liver transplantation (LDLT) has been reported in Japan, Korea, Germany, and other countries, a perfect desensitization protocol has not been established worldwide, especially for patients undergoing simultaneous ABO-i LDLT and splenectomy. We herein report two cases of simultaneous ABO-i LDLT and splenectomy without plasma exchange. One patient had acute liver failure, and the other had hepatocellular carcinoma. To the best of our knowledge, this is the first case report of ABO-i LDLT in China.

Case reports

Two patients underwent ABO-i LDLT on 9 May 2015 and 10 June 2015 at Zhengzhou People's Hospital, Southern Medical University, China (data from China Liver Transplant Registry). This treatment was approved by the Ethics Committee of Zhengzhou People's Hospital according to the principles of the Declaration of Helsinki.

Case 1

A 31-year-old woman underwent ABO-i LDLT for autoimmune hepatitis-induced decompensated liver cirrhosis with acute liver failure. Her notable medical history involved autoimmune hepatitis as defined by the liver diseases criteria of the American Association for the Study of Liver Diseases.[1] Computed tomography images showed liver cirrhosis, splenomegaly, and ascites. A coagulation defect was observed on biochemical analyses, with a prothrombin time of 25 seconds. The total bilirubin (Tbil) concentration was 695 μmol/L, alpha fetoprotein concentration was 6.1 μg/L, and antinuclear antibody titer was 1:640. She had stage 1 encephalopathy due to decompensated liver failure, and her Model for End-stage Liver Disease (MELD) score was 29 before transplantation. Plasma exchange was not performed because her anti-B antibody titer was 1:8 with blood type O Rh(+), but B-type blood plasma was infused every day at 200 ml per day to treat her hypoproteinemia and coagulation disorder 20 days before liver transplantation. The donor was her 46-year-old husband, who had no notable medical history and whose blood type was B Rh(+). LDLT was performed using a left-lobe graft without the middle hepatic vein. After the liver of the recipient had been obtained, University of Wisconsin preservation solution was infused into the graft through the portal vein on the back table. Intraoperative liver wedge biopsy of the donor revealed mild steatosis (7%), and the graft-to-recipient body weight ratio was 1.15% (0.45 kg/39 kg). For the recipient, splenectomy was performed first, and then the disabled liver was resected. Liver transplantation was performed with anastomosis of the hepatic vein to the inferior vena cava and reconstruction of the portal vein and hepatic artery according to LDLT. The operative time for the recipient was 7 hours with a blood loss volume of 2000 ml. B-type blood plasma or O-type white blood cell-filtered red blood cells were infused intraoperatively and postoperatively according to the patient's condition; no signs of incompatibility or allergic blood transfusion reactions were observed. Her anti-B isoagglutinin titers were 1:4 and 1:2 at 3 and 7 days postoperatively, respectively.

Three days postoperatively, pathologic examination of her diseased native liver showed nodular cirrhosis. Her Tbil concentration sharply decreased from 695 to 291 μmol/L on the first postoperative day, then increased to 441 μmol/L on day 7 postoperatively followed by a gradual decrease to 110 μmol/L at 28 days postoperatively. Ten days after transplantation, she developed a mild fever with respiratory distress; these signs combined with lung computed tomography findings were compatible with pulmonary infection. Blood tests showed a white blood cell count of 25×10^9/L, neutrophil level of 87%, platelet count of 195×10^9/L, and procalcitonin concentration of 4.3 μg/L. A sputum culture grew *Staphylococcus aureus* and *Klebsiella* sp., which were treated by meropenem and teicoplanin according to the results of antibiotic susceptibility testing. Her symptoms were gradually resolved, and she completely recovered 14 days after beginning antibiotic administration.

Case 2

A 43-year-old man with liver cancer, cirrhosis, and massive ascites was referred to our center for liver transplantation. His notable medical history included hepatitis B virus-related chronic hepatitis accompanied by hepatitis B surface antigen and hepatitis B core antibody positivity. His preoperative MELD score was 10. The indication for liver transplantation was determined by the Pittsburgh criteria beyond the Milan criteria. Plasma exchange was not performed because his anti-B antibody titer was 1:8 with blood type A Rh(+) before liver transplantation. His 46-year-old wife (AB Rh(+)) offered her right-part liver without the middle hepatic vein. The graft biopsy was normal and the graft-to-recipient body weight ratio was 1.07% (0.55 kg/51 kg). After the spleen and pathological liver were resected, the right hemiliver graft was implanted with reconstruction of the right hepatic vein; meanwhile, end-to-end anastomosis was performed for the corresponding portal veins, right hepatic arteries, and right hepatic ducts. Three days postoperatively, pathologic examination of the excised native liver showed moderately differentiated hepatocellular carcinoma and cirrhosis. AB-type blood plasma was infused intraoperatively and postoperatively, and A-type white blood cell-filtered red blood cells were transfused without signs of incompatibility or allergic blood transfusion reactions. The patient's anti-B isoagglutinin titer was 1:4 at 1 and 2 weeks after the operation. The operative time for the recipient was 8 hours 20 minutes with a blood loss volume of 3000 ml. He received 4000 IU of hepatitis B immunoglobulin during the anhepatic phase of liver transplantation, and his hepatitis B surface antigen titer became negative after transplantation. The prophylaxis schedule was 2000 IU of hepatitis B immunoglobulin daily for the next 6 days, weekly for the following 3 weeks, and then 400 IU for suitable interval days to maintain the hepatitis B surface antibody titer at >500 IU/L within 1 month, 200 IU/L within 6 months, and 100 IU/L thereafter. Entecavir was also administered at 0.5 mg per day to prevent recurrence of hepatitis B virus. His Tbil concentration was mildly increased at 136 μmol/L on day 2 postoperatively, then gradually decreased to a normal level on day 28 after transplantation. The clinical courses of both the donor and recipient were uneventful without any complications.

Immunology protocol and anticoagulant follow-up

To overcome ABO blood type incompatibility, the immunosuppressive regimen included intraoperative induction with basiliximab and methylprednisolone and subsequent immunosuppressive treatment with tacrolimus, mycophenolate mofetil, and

corticosteroids. Within 2 hours before transplantation, 20 mg of basiliximab was administered to the recipient. Before reperfusion of the portal vein, 500 mg of methylprednisolone was infused intravenously; the dose was reduced to 240 mg the day after transplantation and then gradually reduced by 40 mg per day to a maintenance dosage of 20 mg per day. The tacrolimus dosage was adjusted to achieve a trough blood level of 8 to 12 μg/L during the first month and 6 to 10 μg/L thereafter. In Case 1, the tacrolimus dosage was adjusted to maintain a trough blood level of 4 to 6 μg/L during treatment of the pulmonary infection. Mycophenolate mofetil was given at 1 g twice a day, and the dosage was reduced if adverse events such as leukopenia, diarrhea, or infection developed. The anticoagulant protocol included 400 mg per day of xueshuantong injection (key ingredient: *Panax pseudoginseng*) infused intravenously for 2 weeks postoperatively and followed by oral aspirin at 100 mg once a day and oral *Gingko* leaves extract at 300 mg (key ingredient: brass alcoholic glycoside 25 mg) twice a day. The treatments also included antibiotics, antiviral therapy, proton pump inhibitors, and liver-protective medication. On days 1, 3, 7, 10, and 14 after transplantation, Doppler ultrasound revealed adequate liver blood perfusion and favorable transplanted graft characteristics. The patients were followed up regularly according to the China Liver Transplant Registry. No AMR occurred during the 12-month follow-up, and no thrombosis in the hepatic portal system or splenic vein was found.

Discussion

Multiple studies have shown that the long-term graft and patient survival rates of ABO-i recipients are distinctly lower than those of ABO-compatible recipients,[2] for whom the graft survival rates at 1, 3, 5, and 10 years in one study were 71%, 57%, 55%, and 51%, respectively.[3] Many factors contribute to long-term graft and patient survival, but the AMR is the main disadvantage. One report showed that the incidence of AMR was greater if the donor-specific anti-blood group antibody titer was >1:16 at the time of ABO-i liver transplantation. Furthermore, another study showed that when maintaining an anti-ABO titer of <1:32, patient and graft survival were 100% during a 10-month follow-up.[4] Therefore, lower preoperative and postoperative anti-ABO titers are a key to successful ABO-i liver transplantation. If the isoagglutinin titers are high before or after the operation, they should be decreased by plasma exchange or plasma infusion,[5,6] even in the era of rituximab, a B-cell-targeted immunosuppression agent. Patients undergoing ABO-i LDLT who take rituximab also need several series of plasma exchange according to the recipient's isoagglutinin target titer of 1:32.[7] In another report, patients undergoing ABO-i liver transplantation and using rituximab without plasma exchange required intravenous immunoglobulin at the beginning of the operation and continuation for 10 consecutive days after transplantation to prevent AMR.[8] In our patients, the anti-B antibody titers were all 1:8 preoperatively, and B-type blood plasma was infused for 20 days before liver transplantation to ensure desensitization in Case 1. Furthermore, blood plasma without anti-B antibodies was used intraoperatively and postoperatively to maintain the anti-B titer at <1:16 after the operation. Although plasma exchange was not performed, AMR did not occur in the recipients; this may have been a benefit of the lower isoagglutinin titers.

Besides lower isoagglutinin titers, splenectomy and rituximab or basiliximab help to prevent AMR after ABO-i LDLT. Maintenance of an antibody titer of <1:16 during splenectomy with rituximab achieved satisfactory outcomes in a mean follow-up

of 852 days in one report.[9] Additionally, simultaneous splenectomy allowed for safe ABO-i liver transplantation[10] because it helped to modulate the portal flow and immunologic status. The decreased portal venous pressure to avoid a small-for-size graft had beneficial impacts on graft outcomes in left-lobe LDLT.[11] Moreover, splenectomy is necessary for CD138-positive plasma cells remaining in the spleen if rituximab was given just several days before LDLT. Accordingly, 89.5% (17/19) recipients of ABO-i LDLT and 44.7% recipients of non-ABO-i LDLT required splenectomy.[12] However, Ito et al.[13] reported that the incidence of lethal infectious disease was significantly higher in the splenectomy than no-splenectomy group. Meanwhile, the preoperative MELD score was directly correlated with infection, and a MELD score of >20 was associated with early infection after LDLT.[14,15] Studies have also shown that an immunization protocol consisting of rituximab (elimination of CD19+ B cells) can prevent AMR after liver transplantation in blood type-incompatible patients without splenectomy.[8,16,17] In addition, splenectomy did not seem to offer any immunological benefit when the isoagglutinin titer was 1:8. In our recipients, splenectomy was performed before the pathological liver was resected. Patients with a lower anti-B antibody titer may benefit from splenectomy, but the patient in Case 1 developed a bacterial lung infection postoperatively. Considering that the patient in Case 1 had hepatic failure with severe jaundice and a MELD score of 29 and that the patient in Case 2 had a relatively normal immunization with a MELD score of 10 before the operation, simultaneous splenectomy with ABO-i LDLT should be carefully considered in patients with a MELD score of >20. Vaccination reportedly affords partial protection against pulmonary bacterial infection in asplenic patients[18] and has been routinely used to prevent lung infection in LDLT.[12] Although we did not use vaccination in our patients, we believe that it may serve as an effective complementary therapy to lung infection in patients undergoing ABO-i LDLT. The plasma concentration of coagulant and anticoagulant proteins is disturbed after liver transplantation, leading to a hypercoagulable condition that contributes to vascular thrombosis with an incidence rate of 5%.[19] In our cases, however, the anticoagulation protocol involving xueshuantong injection, aspirin, and *Gingko* leaves extract was effective to prevent formation of thrombosis in the hepatic portal system and splenic vein.

Because of the shortage of donor organs, some patients deteriorate further and eventually die while waiting for liver transplantation. If the ABO barrier is overcome, ABO-i LDLT could expand the donor pool from 25% to 35% to offer more opportunity to patients on the waiting list.[20,21] Furthermore, recipients of ABO-i LDLT maybe benefit from a reduced cold ischemia time associated with hepatic function recovery and a longer graft survival time. Our ABO-i LDLT recipients achieved satisfactory outcomes through living-donor grafts, splenectomy, immunosuppression, and anticoagulation. Although the current desensitization protocol unresolved diffuse intrahepatic biliary stricture, an attenuated form of AMR, and although further studies are needed to improve the efficacy of densensitization,[16] ABO-i LDLT with splenectomy is undoubtedly life-saving when an ABO-compatible graft cannot be obtained for patients in critical condition.

Authors' contributions

Chen GY, Sun JJ, Wei SD, Tang GF, Xie ZT, Xu HE, Chen JB, Zhao HB, and Chen YF performed the surgery; Chen GY, Liu GB, Wang B, and Niu B designed the report; and Wang WW and Wei SD acquired the data. Wei SD and Yuan ZH analyzed the data and wrote the paper.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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