SPECIAL ARTICLE

Late Reuse of Liver Allografts from Brain-Dead Graft Recipients: The Munich Experience and a Review of the Literature

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The increasing donor organ shortage requires the consideration of any possible organ donor in order to meet the current demand. However, the growing number of long-term survivors of liver transplantation may create a situation in which former organ recipients may experience brain death with a functioning graft and therefore become organ donors themselves. Previous reports concerning this rare situation predominantly refer to the reuse of donor organs within the first 8 days after primary liver transplantation. So far, only a single case of late reuse of a donor liver has been published, with 2 additional cases mentioned in a summary of the United Network for Organ Sharing database. Here we report the case of a 43-year-old female donor who had received a liver graft for complications of Budd-Chiari syndrome 5 years before becoming an organ donor herself after cerebral infarction with consecutive brain death. ***Liver Transpl 16:701-704, 2010.***

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An increasing imbalance between the number of donor organs and the number of potential liver transplant recipients has led to the development of novel strategies to increase the pool of donor organ donors, that is, the acceptance of extended criteria organs and the technique of liver graft splitting.[1] Consequently, the acceptance of liver allografts from brain-dead individuals who previously underwent transplantation has also become a potential option to extend the number of liver donors.[2] The immediate reuse (within hours or days) of liver allografts retrieved from liver graft recipients who suffered brain death during or shortly after liver transplantation has been reported previously.[3-6] However, only a few reports describe the reuse of a previously transplanted liver graft years after initial transplantation.[7] This situation may be expected more frequently as more graft recipients may die with functioning grafts, especially with functioning liver grafts. Here we provide detailed insight into a case in which a patient received a liver graft from a former recipient who became an organ donor after a cerebrovascular accident that occurred 5 years after primary liver transplantation.

CASE REPORT

First Transplant

The donor liver was procured in 2003 from a 16-year-old girl with a body mass index of 24 kg/m^2 (63 kg and 163 cm). Brain death developed after intoxication with valproic acid in a suicide attempt. Seventeen hours before organ donation, craniotomy was

Abbreviations: CMV, cytomegalovirus; MELD, Model for End-Stage Liver Disease.
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performed for cerebral pressure relief without reconstitution of brain function. The blood group was B rhesus-positive. Except for a positive finding for cytomegalovirus (CMV) immunoglobulin G, no antibody formation against hepatitis A, B, or C, human immunodeficiency virus, or syphilis was identified. Blood chemistry tests revealed normal results for electrolytes, renal and liver function tests, and coagulation tests. The donor presented in a stable cardiopulmonary condition (the blood pressure ranged from 100/86 to 150/100 mm Hg, and the maximum heart rate was 130 bpm). The body temperature was elevated to 41°C prior to organ donation. University of Wisconsin solution was used for graft preservation.

The first recipient of the liver allograft was a 38-year-old woman who underwent transplantation in June 2003 because of liver failure due to Budd-Chiari syndrome. Her blood group was donor-identical and B rhesus-positive. The transplantation procedure was uneventful. Vascular reconstruction included a piggyback vena cava anastomosis and a side-to-end arterial anastomosis between the common hepatic artery (donor) and the bifurcation of the proper hepatic artery and gastroduodenal artery (recipient). The portal vein and common bile duct were reconstructed with a standard end-to-end technique.

The patient recovered rapidly from transplantation and was discharged 3 weeks later. After liver transplantation, heparin-induced thrombocytopenia was managed successfully by a switch to lepirudin as an anticoagulant. Immunosuppression was maintained with cyclosporine A; the initial additive immunosuppressants prednisolone and mycophenolate mofetil were discontinued 6 months after transplantation. Besides enalapril, metoprolol, and spironolactone, concomitant medication included phenprocoumon (to prevent recurrence of Budd-Chiari syndrome).

Second Transplant

In May 2008, the liver recipient developed thrombosis of the cerebral artery. Treatment was complicated by the development of a cardiac thrombus 6 days after admission, which led to cardiac arrest requiring cardiopulmonary resuscitation for 10 minutes. Thereafter, the patient showed a completely stable cardiopulmonary status, with a blood pressure of 110/60 mm Hg at a heart rate of 110 bpm, a body temperature of 37.7°C, and no evidence of peripheral embolization. The patient had previously consented to organ donation, and this was confirmed by her relatives after brain death was evident and diagnosed. Blood chemistry results revealed no hepatic injury post-resuscitation; ultrasound of the liver showed normal parenchymal texture and a regular flow pattern in the portal vein and the hepatic artery (resistive index = 0.52). Serology tests for antibody to hepatitis B surface antigen, hepatitis B core antigen, hepatitis C virus, human immunodeficiency virus, and CMV were negative, and only anti-immunoglobulin G antibodies against syphilis were positively detected. Preservation was performed with histidine tryptophan ketoglutarate (8000 mL) after anticoagulation with 16 mg of Refludan (because of the previously detected heparin-induced thrombocytopenia). According to the standard procurement technique, the vena cava was retrieved, and this included the vena cava segments of the first and current donors. The former arterial anastomosis and parts of the initial recipient celiac trunk were preserved in continuity.

A 51-year-old blood group-identical woman was identified by Eurotransplant as the second graft recipient in May 2008. Suffering from progressive polycystic liver disease, this patient was listed for liver transplantation in May 2003 (body mass index = 26.9 kg/m^2). Her Model for End-Stage Liver Disease (MELD) score at the time of transplantation was calculated to be 9, and the inclusion of standard exceptional MELD points for the underlying disease led to a score of 24. During back-table preparation, all vascular and biliary structures were identified and carefully dissected. Fresh-frozen histological examination of liver specimens was performed to exclude severe preexisting graft injury. The detection of microvesicular steatosis in 40% of the hepatocytes prompted us to proceed with transplantation. During recipient hepatectomy, a portocaval shunt with complete preservation of the inferior vena cava was used as described earlier.[7,8] The luminal orifices of the suprahepatic and infrahepatic vena cava segments were closed with running sutures (Prolene 4-0). Partial side clamping of the recipient vena cava allowed a side-to-side cavocavostomy with running sutures (Prolene 4-0). The reconstruction of the hepatic artery was established between the bifurcation of the common hepatic artery (recipient) and a small patch consisting of parts of the gastroduodenal and common hepatic arteries (graft); this procedure was performed to exclude narrowing of the anastomosis. After completion of all vascular anastomoses, reperfusion was enabled simultaneously via the portal vein and hepatic artery. An end-to-end anastomosis immediately below the confluence of the right and left hepatic ducts served for biliary tract reconstruction. The times for surgery and cold and warm ischemia were 308, 633, and 40 minutes, respectively. The blood transfusion requirement included 3 U of packed red cells and 15 U of fresh-frozen plasma; 1100 mL of cell saver blood was retransfused during surgery.

Postoperative recovery was completely uneventful with a rapid normalization of liver function tests and blood chemistry results. The patient was treated under intensive care for 5 days after transplantation. Immunosuppression was initiated 1 day after transplantation with tacrolimus and prednisone. Six weeks thereafter, the application of prednisone was discontinued after tapering. The patient was discharged from the hospital on postoperative day 8.

The patient has been closely followed up for 1.5 years after transplantation. To this date, no serious events have been registered. CMV activation, with a maximum number of 3210 copies/mL, was successfully treated with valganciclovir for a period of 6

weeks. Liver function tests returned to normal ranges within the first 3 postoperative days after peak levels of 667 and 307 U/L were reached for aspartate aminotransferase and alanine aminotransferase, respectively.

DISCUSSION

Organ donor shortages represent one of the major problems in organ transplantation. Currently, the number of liver allografts does not meet the number needed to supply all patients suffering from terminal liver disease on the waiting list, and this has resulted in a waiting list mortality rate of approximately 24% within 3 years.[9] Widening the donor pool by the extension of the acceptable donor criteria to include so-called extended donor criteria may be one option.[2] However, the brain death of a former organ recipient is still a rare event. The likelihood of this situation may increase with the growing number of organ recipients who experience long-term survival. Several reports have documented the feasibility of transplanting solid organs derived from graft recipients who became donors.[10] Nevertheless, most of these reports refer to repeated transplantation of grafts within hours or days after initial transplantation when brain death of the recipient occurred in the early postoperative phase.[3-6] In contrast, the late reuse of liver grafts has only rarely been reported in the past. Recently, the French group led by Daniel Cherqui[7] reported the reutilization of a liver graft that was transplanted 13 years before the second graft procurement in the first recipient with a completely uneventful posttransplant course. This led others to review the United Network for Organ Sharing database to identify comparable cases in North America. Between 1993 and 2000, only 2 liver transplants using donor organs from long ago transplanted liver recipients were registered in the United Network for Organ Sharing region.[3] However, no detailed information about the organ selection processes and donor history was reported for these cases. One of the reported grafts demonstrated normal liver function after 176 days; the second graft failed 3 days after transplantation.

The patient presented in this case report has shown perfect graft function without any signs of general or organ-specific deterioration 1.5 years after transplantation. Only a CMV infection without signs of CMV disease, detected in routine serology testing, occurred, and it was successfully treated with ganciclovir.

Although the histological evaluation at the time of transplantation revealed no signs of structural organ injury, it remains impressive how quickly the graft recovered postoperatively when we consider a second immunological event in the lifetime of the graft. Hepatocellular enzyme release peaked 2 days after transplantation, and the bilirubin serum level never exceeded 5.3 mg/dL. The liver graft revealed histological evidence of microvesicular steatosis in 40% of the hepatocytes of the graft without signs of macrovesicular steatosis. We therefore decided to continue with the procedure, particularly because we had previously shown that acceptable posttransplant results can be achieved with grafts showing up to 60% microvesicular steatosis.[11] Apart from that, we believe that histological exclusion of graft abnormalities is mandatory in the case of graft reuse; this is similar to the situation with extended criteria donor organs. Our policy includes the delay of anesthesia introduction until a pathological result is obtained and, if necessary, interruption of the transplantation procedure. However, it remains speculative whether or not the reuse of a liver makes the graft more vulnerable to ischemia/reperfusion injury and potentially leads to a higher degree of steatosis or a worse outcome in comparison with regular deceased donor grafts. Nevertheless, until further experience is gained with reused liver grafts, we would recommend the classification of these grafts as extended donor criteria grafts with all potential limitations for transplantation in patients with a MELD score higher than 25.

Nevertheless, repeated transplantation of a single liver graft in 2 different recipients may represent a technical challenge and thus increase the risk for the recipient. First, the previously performed vascular anastomoses have to be identified during the donor operation and carefully dissected during cold preparation; this allows precise length adaptation of the portal vein length during implantation with intended resection of the primary anastomosis to avoid segmental stenosis. Second, in our case, we performed a side-to-side cavocavostomy, as described in principle by Belghiti et al.[8] and more recently by Tayar et al.[7] in the case report from Paris. Because the first transplant was also performed with a piggyback technique (preservation of the recipient vena cava), the present vena cava anastomosis consisted of 3 layers of venous tissues (2 donors and the recipient). Arterial reconstruction in general should not represent a major problem because the graft itself still provides sufficient arterial length; alternatively, the celiac trunk of the first recipient (now the donor) can be used. If for any reason the anatomic situation or the arterial supply of the graft is in danger, we prefer the interposition of a jump graft between the aorta and the hepatic artery of the graft (ie, by interposition of donor-derived iliac vessels).

Biliary reconstruction remains an Achilles' heel in liver transplantation, particularly when a liver graft is used for the second time. In most cases, the former biliary anastomosis (first transplant) is surrounded by scar tissue, and this presents some uncertainties in terms of the local blood supply. In general, the arterial biliary blood supply predominantly originates from the hepatic artery. However, in our particular case, the initial biliary anastomosis could not be identified. Thus, to avoid segmental ischemia of the biliary reconstruction, connective tissue surrounding the biliary tract was spared from dissection. In addition, the graft-side bile duct was shortened to its bifurcation to eliminate an inadequately arterialized bile duct segment. Nevertheless, because of the individual

situation for other patients, choledochojejunostomy may represent the safer option for reconstruction. Besides technical threats, the influence of chronic immunosuppression on reused liver graft function remains one of the unanswered questions. In our case, histological examination did not reveal any signs of calcineurin inhibitor-induced chronic vascular changes. Reports about long-term toxic side effects of immunosuppressants in liver transplants are rare in the literature, and calcineurin inhibitor-related vasculopathy may not even be expected with liver transplants, in contrast to kidney transplants. It could rather be speculated that chronic tacrolimus exposure may exert a certain protection against ischemia and reperfusion-related, survival-compromising signaling and reduce cell death and thus may lead to superior graft function.[12,13]

This detailed documentation of a case of liver graft reuse for a second organ recipient years after the first transplant supports the conclusions of the French group at Mondor Hospital in Creteîl: this strategy is definitely feasible, and recipient-derived donor organs may not necessarily be considered extended donor criteria grafts. Because experience with reutilization of recipient-derived donor organs remains limited, an individual decision concerning organ acceptance and surgical technique is recommended, particularly in liver transplantation.

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