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ORIGINAL ARTICLE

Novel rescue procedure for inferior vena cava reconstruction in living-donor liver transplantation using a vascular graft recovered 25 h after donors' circulatory death and systematic review

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deceased donor, graft, inferior vena cava reconstruction, living-donor liver transplantation, vessel graft.

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Summary

Liver transplantation is a lifesaving treatment for patients suffering from end-stage liver disease. Rarely, acute congestion of the inferior vena cava (IVC) is being encountered because of tumor compression. MELD allocation does not reflect severity of this condition because of lack of organ failure. Herein, a patient is being presented undergoing urgent living-donor liver transplantation (LDLT) with IVC reconstruction for a fast-growing hepatic epithelioid hemangioendothelioma (HEH). IVC reconstruction using a venous graft recovered from a 25-h after circulatory-death prior transplantation became necessary to compensate severe venous congestion. Additionally, a systematic review of the literature searching MEDLINE/PubMed was performed. Protocol and eligibility criteria were specified in advance and registered at the PROSPERO registry (CRD42013004827). Published literature of IVC reconstruction in LDLT was selected. Two reports describing IVC reconstruction with cryopreserved IVC grafts and one IVC reconstruction using a deceased after-circulatory-death-donor IVC graft were included. Follow-up was at 12 and 13 months, respectively. Regarding the graft recovery in the setting of living-related donation, this graft remained patent during the nine-month follow-up period. This is the first report on the use of a venous graft from a circulatory-death-donor, not eligible for whole organ recovery. We demonstrate in this study the feasibility of using a size and blood-group-compatible IVC graft from a cold-stored donor, which can solve the problem of urgent IVC reconstruction in patients undergoing LDLT.

Introduction

Hepatic epithelioid hemangioendothelioma (HEH) is a rare tumor of vascular origin carrying an unpredictable malignant potential. Its incidence is one in a million [1]. Treatment remains controversial and is limited because of the nature of this particular tumor, that is, size, location, speed of growth, and late diagnosis. Literature describes liver resection, liver transplantation, and chemotherapy as treatment options [2–4]. Removal of retrohepatic inferior vena cava (IVC) is frequently mandatory for oncological reasons: vascular invasion or proximity of residual tumor to IVC or diffuse and multifocal tumor [5].

While IVC replacement is not an issue in standard deceased liver transplantation, living-donor liver transplantation (LDLT) requires reconstruction of the retrohepatic vena cava by either autologous, cryopreserved allogeneic, or synthetic vascular grafts. Use of allografts in the very

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beginning of liver transplantation has been described by Starzl *et al.* Preservation and storage procedures for such grafts have been described by Starzl *et al.* [6] and Martinez *et al.* [7].

This study presents a novel rescue procedure and reports the case of a woman with newly diagnosed HEH and progressive tumor obstruction of the IVC. The patient underwent urgent LDLT with reconstruction of the IVC using a venous graft, recovered from a 25-h deceased donor in a close by but foreign hospital. Furthermore, we performed a systematic review of the literature assessing: (i) the feasibility of IVC reconstruction using deceased donor vascular grafts, (ii) the association of complications in IVC reconstruction, and (iii) the potential complications associated with the use of deceased donor grafts.

Material and methods

Case report

A 45-year-old woman with a known HEH was admitted to the emergency department with severe abdominal pain, progressive edema of the lower extremities, and elevated cholestatic parameters and pancreatic enzymes. Ultrasonography and computed tomography (CT) showed a diffuse liver tumor of unknown origin with dilatation of the intrahepatic biliary tree (Fig. 1a). The liver tumor was considered unresectable as a result of the involvement of all hepatic veins and portal bifurcation. Transjugular liver biopsy failed to prove malignancy, showing only nonspecific inflammatory reaction of the liver. At that time, the differential diagnosis was giant hemangioma or hepatic sarcoma. MRI with repeated tumor biopsy was planned and revealed HEH with strong CD34 positivity. Liver transplantation was regarded as the only remaining treatment option because of diffuse tumor spread within the liver and the absence of extrahepatic disease. Decision for deceased donor, orthotopic liver transplantation (OLT) was accordingly made. The patient was listed for deceased donor OLT, and the alternative of LDLT was discussed with the patients' family to shorten waiting time.

The patients' husband was hospitalized for predonation checkup. Simultaneously, the patient was admitted with persisting and severe abdominal pain, anxiety, nausea, and acute onset of severe cava congestion. MRI showed progressive tumor growth with subtotal compression and potential invasion of the vena cava. Because of the rapid worsening of the patients' condition and a lack of suitable donors, we opted for LDLT after completion of the predonation checkup of the patients' husband. However, we failed to identify a blood-group-compatible vascular graft in our graft bank. Replacement of the IVC by synthetic grafts was discussed, but regarded as disadvantageous because of increased risk of thrombosis and infections [8].

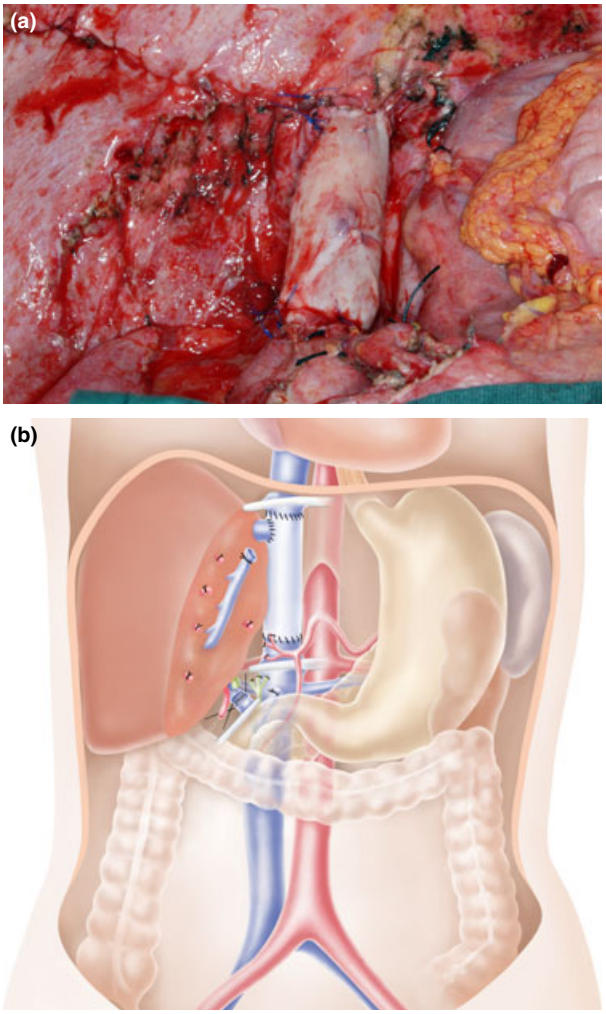

Figure 1 (a, b) Reconstruction of the resected vena cava by an inferior vena cava graft recovered 25 h after donors' circulatory death (end to end) and implanted right hemiliver. (Graphics by Stefan Schwyter).

Surgical technique

Urgent LDLT with IVC reconstruction was necessary. In the absence of matching grafts, an alternative was discussed. We proceeded to recovery of a portion of an IVC (8 cm in length) from an 80-year-old blood-group-matched donor (A+ both donor and recipient) who had died 25 h before because of chronic obstructive pulmonary disease. He had been stored at 4 °C in the pathology department. A history of malignancy, bacterial, and viral infection (negative serology for hepatitis A, B, and C, and HIV) was excluded, and informed consent was taken from his relatives. Recovered IVC was cold preserved in Celsior® solution (Genzyme Corporation Cambridge, MA, USA).

Transplantation started on the recipient to exclude extrahepatic manifestation of the disease. Intra-operatively,

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invasion of the cava was strongly suspected as well as an invasion of the tumor in the right part of the diaphragm. Frozen section samples were tumor negative. Total hepatectomy was performed including resection of the retrohepatic vena cava and a part of diaphragm, thus achieving complete tumor removal. Reconstruction of retrohepatic IVC was then performed with interposition of vascular graft using continuous sutures with 6–0 Prolene (Fig. 1a). Simultaneously, right lobe donor hepatectomy was performed. After graft flushing, hepatic vein was anastomosed with the interposed cava graft. Afterward, the implanted partial liver graft was reperfused, and the bile duct was anastomosed end to end (Fig. 1b).

Systematic review

Protocol and registration

The protocol and inclusion criteria were specified in advance and registered at the PROSPERO international registry of systematic reviews (CRD42013004827) [9].

Eligibility criteria

Inclusion criteria: All published case series, case reports, potential randomized controlled trials (RCT), prospective and retrospective comparative cohort studies, and case-control studies where used for the qualitative synthesis of the systematic review. No year or language limitations were considered. Published literature using the MEDLINE/PubMed database was searched until March 2013

To enter the analysis, studies had to fulfill the following criteria: adult patients receiving a living liver transplantation including IVC graft used for retrohepatic IVC reconstruction.

Exclusion criteria: Studies that failed to fulfill the inclusion criteria were excluded. In addition, studies were excluded by the following criteria: studies including children or adolescents (under the age of 18 years), animal studies and studies reporting the use of autologous or synthetic grafts.

Study selection

A systematic review of the literature was performed to identify all studies published reporting IVC reconstruction in LDLT with IVC graft. The systematic review protocol was registered to the PROSPERO registry and is available at: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42013004827.

For detailed Search terms see also the Supplementary Methods.

In addition, the reference lists of relevant articles were screened to capture any potential articles not identified by the MEDLINE search.

Data extraction

Abstracts were used to identify suitable articles. All extracted literature and their information were recorded in a standardized form by two reviewers independently (AFP and DE). Full texts of papers considered suitable for inclusion were accessed for further evaluation and selection. All articles that did not include cases of reconstruction of IVC by deceased donor IVC graft were excluded. Relevant data were obtained from full texts of all selected papers by two authors (AFP and DE): Origin of the IVC graft, storage and preservation solution, length of IVC graft, donor demographics, recipients' demographics, underlying disease of the recipient, duration of operation, postoperative course, length of hospital stay (LOS), and patient follow-up. Any differences were settled by consensus (Supplementary tables and figures, Figure S1). This study was reviewed by the ethics committee and performed in accordance with the ethical standards of the 2000 Declaration of Helsinki as well as the Declaration of Istanbul 2008. The relatives of the donor gave their informed consent prior to study inclusion.

Outcomes of interest

The primary outcome measure was complications related to the IVC graft. Secondary outcomes were the graft and patient survival as well as the feasibility of the surgical technique.

Results

Case report

The transplant procedure lasted 9 h, and the patient was transfused with one packed red blood cells. The patient was discharged at day 15. Both donor and recipient had an uneventful recovery. The histological assessment of the resected liver confirmed tumor in the resected vena cava and multiple intrahepatic microvascular invasion. Immunosuppression was initiated with tacrolimus and steroids, and switched two months later to a mTOR inhibitor (Everolimus, Novartis, Basel, Switzerland) because of its known anti-angiogenic effects [10]. Nine-month imaging follow-up was uneventful with full recovery of the patient and normalized laboratory values after six months. Control MRI confirmed a regenerated right hemiliver with patent right and middle hepatic veins and reconstructed cava segment. A small thrombus of 4 mm in the IVC at the level of the hepatic vein bifurcation subsided successfully with Dalteparin s.c. treatment. The donor's postoperative course remained uneventful. The left lobe of the remnant liver

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showed acceptable size (85% in volumetric imaging) after 3-month follow-up.

Systematic review

A total of 1162 potentially eligible articles published were identified from literature searches. After screening on eligible criteria, 15 were selected for full-text review. Of these, 12 were further excluded following full-text review. Three studies matched the selection criteria. Both case series ($n = 2$) [11,12] and case reports ($n = 1$) [13] were retrieved and describe the reconstruction of IVC in LDLT with IVC graft. In two cases, a cryopreserved vessel was used, and in one case, an IVC graft recovered after donors' circulatory death was utilized for reconstruction. Identified cases were published between 2004 and 2010. In all the three cases, retrohepatic IVC was involved by hepatocellular carcinoma (HCC) tumors reporting requirement of resection and reconstruction of IVC during transplantation.

At 12- and 13-month follow-up periods, the grafts remained uneventful. Regarding the surgical technique in our study, the deceased donor cava graft remained patent during the nine months of follow-up.

Authors of suitable articles were contacted to provide more detailed data. Because of lack of reply, data could only be obtained from one author for further evaluation [13]. Characteristics of the studies are summarized in the Supplementary tables and figures section in Table S1.

Discussion

Venous grafts from cold-stored donors 25 h after circulatory death can be used successfully as IVC conduits either in liver transplantation or extended liver resection cases. To the best of our knowledge, recovery of human venous grafts 25 h after circulatory death for later reconstruction of the recipients' vena cava has never been described. The presented case refers to a young female patient suffering from a newly diagnosed HEH with severe obstruction of the retrohepatic vena cava. Liver resection and OLT achieve comparable results in HEH treatment [14]. Because of the hypertrophy of segments 2 and 3, a trisectionectomy was not indicated because of the involvement of the portal vein and the left hepatic vein (Supplementary tables and figures, Fig. 2). Despite suspected IVC invasion, liver transplantation was regarded as feasible approach, and no other options were considered suitable. As our allocation system is based on the model of end-stage liver disease (MELD) system, listing for liver transplantation in tumor situations results in 14 exceptional points (in Switzerland given for the tumor situation). One point per month waiting time will be added. Our patient was admitted with acute onset of severe cava congestion without the presence of encephalopathy. Super urgent listing for OLT was not possible because of full hepatocellular function. Therefore, the only alternative procedure at that time was LDLT. Accordingly, we searched for reconstruction modalities of the vena cava in the setting of LDLT. Various options are reported:

First, LDLT with cava reconstruction using banked or freshly procured venous grafts from deceased donors,

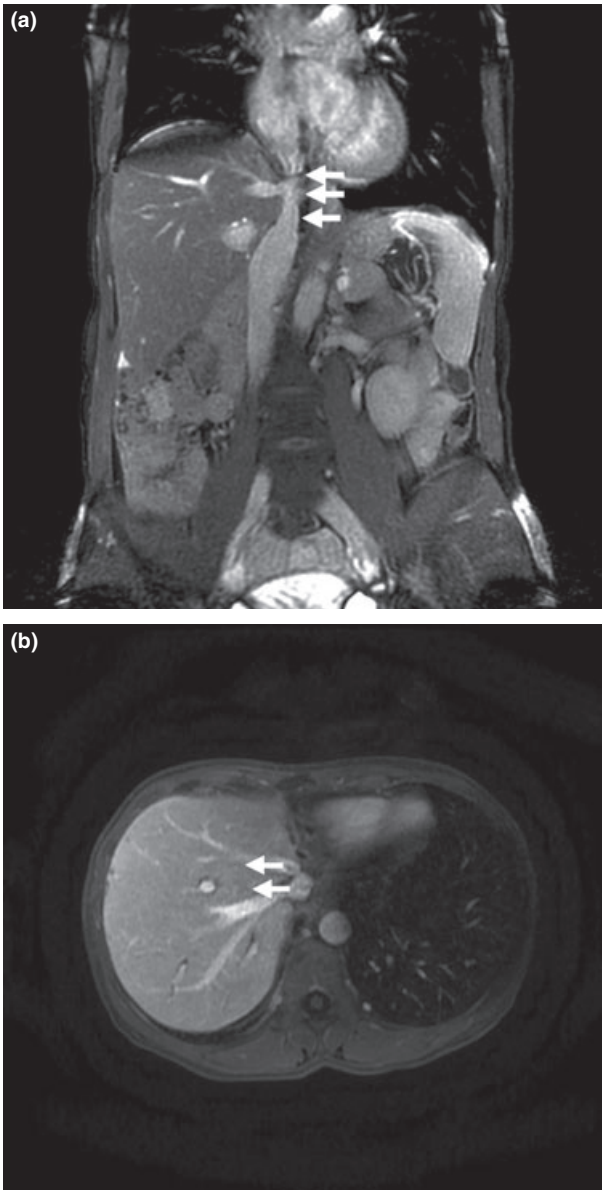

Figure 2 (a, b) Follow-up 9 months after living-donor liver transplantation showing a regenerated right hemiliver, normal perfused right and middle hepatic veins (arrows), and vena cava interponat. A small thrombus of 4 mm in the inferior vena cava at the level of the hepatic vein bifurcation was successfully treated with Dalteparin.

derived from the donor or recipient (internal jugular vein, iliac vein, portal vein, or saphenous vein) [7,12,15–18]. However, no banked vessels were available at that time, either at our center or the rest of the country. Second, synthetic grafts have also been used [19], but are more prone to thrombosis or infection [8].

Numerous techniques related to the use of preserved vascular allografts have been described. Nowadays, the iliac vessels are routinely been explanted during multi-organ recovery after donors' circulatory death. As donor or recipient vessel reconstruction during transplant procedure may become necessary. It is common practice to use the donor iliac artery Y-graft to reconstruct the pancreas allograft arterial anatomy before implantation procedure. In liver transplantation, it is a common procedure to use iliac vessels for both arterial and portal vein reconstruction and for renal transplants if indicated [20].

Use of deceased donor iliac arterial conduits for hepatic allograft vascular reconstruction has been encouraging, with good initial technical success rates and long-term graft survival [7,20]. Although IVC replacement is necessary in patients with Budd–Chiari syndrome, there are hardly any graft vessels available for IVC reconstruction during LDLT [21]. However, the knowledge gained from these settings has not been transferred to liver transplantation overall. Therefore, the presented rescue procedure can be an option in such desperate surgical cases.

Since the early attempts of Alexis Carrel a decade ago on preservation of vessels and organs, it is known that vascular structures may tolerate even longer period of warm and cold ischemia [22]. Therefore, the idea was proposed to recover an IVC from a cold-stored deceased male donor kept in the pathology department for 24 to 48 h at 4 °C.

It is common practice to recover femoral arteries and veins from donors after cardiac death. To minimize postmortem autolysis and bacterial translocation, such vessels are recovered as soon as possible after death [23]. If the deceased donor is temporarily stored at 4 °C, customarily done in many hospitals before funeral, no standard recommendation exists regarding a safe time span extension following cardiac death until procurement of vascular grafts. One experimental study from 1991 reported on aortic graft recovery in sheep after 24 h and 48 h storage at 4 °C following donor death showing that even a 48 h delay between donor death and graft retrieval did not result in a significant effect on conduit function in the recipients [24,25].

There is risk of thrombus with any type of vascular grafts especially with synthetic grafts [10]. In tumor resection cases, contaminated tissue beds and low flow thrombogenicity may limit the use of synthetic prostheses. We opted against synthetic vascular graft reconstruction because of its known risks of infection. Decision for biological allograft was taken because of its durability and versatility of the tissue substance. Furthermore, biological allografts are considered first choice for venous reconstruction [26]. In the present report, the patient developed a small thrombus of 4 mm in the IVC at the level of the hepatic vein bifurcation. However, this did not affect our patients' course.

Systematic review of the literature confirms that a reconstruction of retrohepatic IVC by a deceased donor graft is an applicable technique but also an aggressive approach in cases with unresectable tumors involving adjacent structures of the liver. In all of the matching articles, HCC was the indication for LDLT. Two studies replaced the retrohepatic IVC by a cryopreserved graft [11,12]. Recipients follow-up shows positive outcome with no postoperative complications reported. In the most comparable study to our case, IVC graft was recovered preemptively from a brain death donor and stored for 48 h until planed LDLT was performed [13]. Postoperative course of the recipient reported no complications. The patient died eight years after surgical procedure of recurrent HCC tumor.

Patients with benign tumors and tumors involving the retrohepatic IVC are usually excluded from the waiting list for organ transplantation. Therefore, the presented technique for LDLT with necessary reconstruction of retrohepatic IVC is an applicable option and may lead to acceptable outcomes.

We demonstrate in this study the feasibility of using a size and blood-group-compatible IVC graft from a cold-stored donor, which can solve the problem of urgent IVC reconstruction in adult patients undergoing LDLT. No specific vascular graft complications occurred.

This study has some limitations. The recovery of a venous graft form a donor 25 h after circulatory death may not be feasible in some countries. For the systematic review, no other database than MEDLINE/PubMed was searched. This could be considered as publication bias. However, this is a very specific topic that has only been described in a total of three published cases. Furthermore, the patient did not consent to receive a venous graft from a cold-stored donor. This fact may have medicolegal implications, especially in case of complications. Thus, we suggest that this should be included into the informed consent if there is even a low possibility of using such a graft. Even though the donor was tested for infections in existing preserved serum, this may not be available in some cases. Tests may not be reliable in the case of recent infections. This should be taken into consideration and should be included into the informed consent.

In conclusion, the reconstruction technique of the retrohepatic IVC by a deceased and cold-stored donor graft might well be helpful in very highly selected cases and may enlarge the donor pool for vascular allografts in the urgent

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setting of unavailable vessel grafts in desperate surgical situations. We do not find any associated graft complications, and the patient showed optimal outcome.

Authorship

AFP: drafted the manuscript, collected the patient data, and screened the literature for eligible records. CEO OR, DD, and ML: drafted the manuscript. DAR: designed the systematic review protocol and drafted the manuscript. DE: screened the literature for eligible records. AS: drafted the manuscript and assisted designing the systematic review. PD: developed the surgical technique and drafted the manuscript. PAC: drafted the manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Flow diagram showing study selection process of the systematic review of the literature.

Table S1. Overview of included studies

Data S1. Methods

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