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Assessing the Safety of Expanded Polytetrafluoroethylene Synthetic Grafts in Living Donor Liver Transplantation: Graft Migration Into Hollow Viscous Organs – Diagnosis and Treatment Options

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Background: Our recent studies have highlighted the importance and safety of backtable venoplasty for middle hepatic vein (MHV) and inferior right hepatic veins (IRHV) reconstruction using expanded polytetrafluoroethylene (ePTFE) vascular grafts. In this study, we aim to analyze the complications associated with ePTFE graft use and discuss the management of the rare, but, potentially life threatening complications directly related to ePTFE conduits.

Material/Methods: From January 2012 to October 2015 a total of 397 patients underwent living donor liver transplantation (LDLT). The ePTFE vascular grafts were used during the backtable venoplasty for outflow reconstruction in 262 of the liver allografts. Recipients who developed ePTFE-related complications were analyzed.

Results: ePTFE-related complications developed in 1.52% (4/262) of the patients. One patient (0.38%) developed complete thrombosis with sepsis at 24 months post-transplantation and died due to multiorgan failure. Three patients (1.1%) developed graft migration into the second portion of the duodenum, without overt peritonitis. Surgical exploration and ePTFE graft removal was done in all the patients. One patient died due to overwhelming sepsis.

Conclusions: ePTFE graft migration into the duodenum causing perforation is a new set of complications that has been recently described in LDLT and can be treated effectively by surgical removal of the infected vascular graft and duodenal perforation closure. Despite of such complications, in our experience, ePTFE use in LDLT continues to have wide safety margin, with a complication rate of only 1.52%.

MeSH Keywords: Living Donors • Liver Transplantation • Polytetrafluoroethylene

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Background

Reconstruction of the anterior sector venous drainage of a right liver allograft remains an important step during backtable venoplasty in a right-lobe LDLT that prevents postoperative congestion and graft dysfunction. Interpositional vascular grafts are often necessary to accomplish the venoplasty to form a common outflow channel that facilitates outflow reconstruction. Various types of vascular grafts can be used as conduits for backtable venoplasty, such as cryopreserved venous grafts, recipient umbilical vein (in certain situations), donor or recipient autologous veins, or ePTFE synthetic grafts. However, the cryopreserved vascular graft supply is scarce in Asia due to limited numbers of deceased donor transplantations. Although the autologous veins can also be obtained from donors or recipients, it increases surgical complexity and entails more blood loss. Hence, many transplant centers, including ours, have resorted to use ePTFE synthetic vascular grafts for reconstruction of MHV tributaries and IRHVs, with acceptable patency rates and excellent graft outcomes [1–3].

Although the safety of ePTFE synthetic vascular grafts in LDLT has been proven, complications such as graft thrombosis and infection are the major concerns in using such grafts. In recent years, a rare complication of hollow viscous migration of the ePTFE graft has been reported [4–7]. The graft migration into the surrounding hollow viscous organs may lead to peritonitis and/or septicemia due to infection of the graft, thereby increasing the risk of mortality. Hence, timely diagnosis and prompt surgical management must be instituted to remove the migrated vascular graft. However, the experience and exact management protocol in this regard remain limited. In this retrospective analysis, we assessed the complication profile of ePTFE graft use and its feasibility in LDLT. We also aimed to describe the management protocol for ePTFE graft migration into adjacent hollow viscous organs in LDLT recipients.

Material and Methods

From 1 January 2012 to 31 October 2015, a total of 397 recipients underwent LDLT at China Medical University Hospital; 262 patients received right liver allografts devoid of MHV that required backtable reconstruction of MHV tributaries and/or IRHVs using ePTFE synthetic grafts.

The intraoperative and postoperative data of these patients were assessed for the outcome and ePTFE-related complications during the post-transplant period. We retrospectively analyzed data from recipients who developed ePTFE graft thrombosis causing liver outflow obstruction, infection of the ePTFE graft leading to sepsis, and graft migration into the adjacent hollow viscous during the post-transplant period. Four recipients (n=4) who developed ePTFE graft thrombosis and migration of the ePTFE graft into the surrounding hollow viscous organs were further studied.

The demographic data, preoperative diagnosis, and postoperative follow-up data of these recipients were collected. Clinical symptoms and progress of the recipients after diagnosis of complications were noted. All the recipients in this study were hospitalized after detection of the complication(s).

Description of the backtable venoplasty technique of our institution is beyond the scope of this article and was described earlier in detail [3,8]. Figure 1 shows various backtable venoplasty procedures used to reconstruct the MHV and/or IRHV tributaries. All the venous tributaries on the cut surface of liver allograft and the IRHVs of 4 mm or more in diameter were reconstructed. In the present cohort, outflow reconstruction was done by use of the following techniques:
1. "Single Oval Ostium" technique [9] in patient 1.
2. MHV reconstruction using ePTFE graft in patient 2.
3. Bridging conduit plasty [10] in patient 3.
4. "V-plasty" technique [3] in patient 4.

All the recipients received ampicillin 1 g intravenously 4 times a day and cefotaxime 2 g intravenously 3 times a day for 5 days during the postoperative period [3]. An antiplatelet aspirin 100 mg QD was given to all the recipients who received liver allografts with ePTFE from the 5th post-transplant day, and continued for 2 years.

Postoperative imaging protocol

Postoperative ultrasonography (USG) study of the abdomen was done on the 1st, 4th, and 7th postoperative days after transplantation and then weekly thereafter for the 1st month to evaluate graft tissue perfusion, venous outflow, and graft regeneration. For the recipients who received right liver grafts with backtable venous reconstruction by "V-plasty" [3], a follow-up computed tomography (CT) scan of the abdomen was performed during the 3rd postoperative month, while a CT scan was performed for other recipients only when deemed necessary.

Results

Out of 262 patients who received right liver allografts with ePTFE vascular grafts, 4 patients (1.52%) developed ePTFE graft-related complications that required hospitalization and surgical intervention. One patient in this series developed complete thrombotic occlusion of the ePTFE graft that extended up to the inferior vena cava (IVC) with infection and sepsis leading to liver allograft dysfunction (0.38%), and 3 patients (1.1%) developed ePTFE graft migration into the second portion of the

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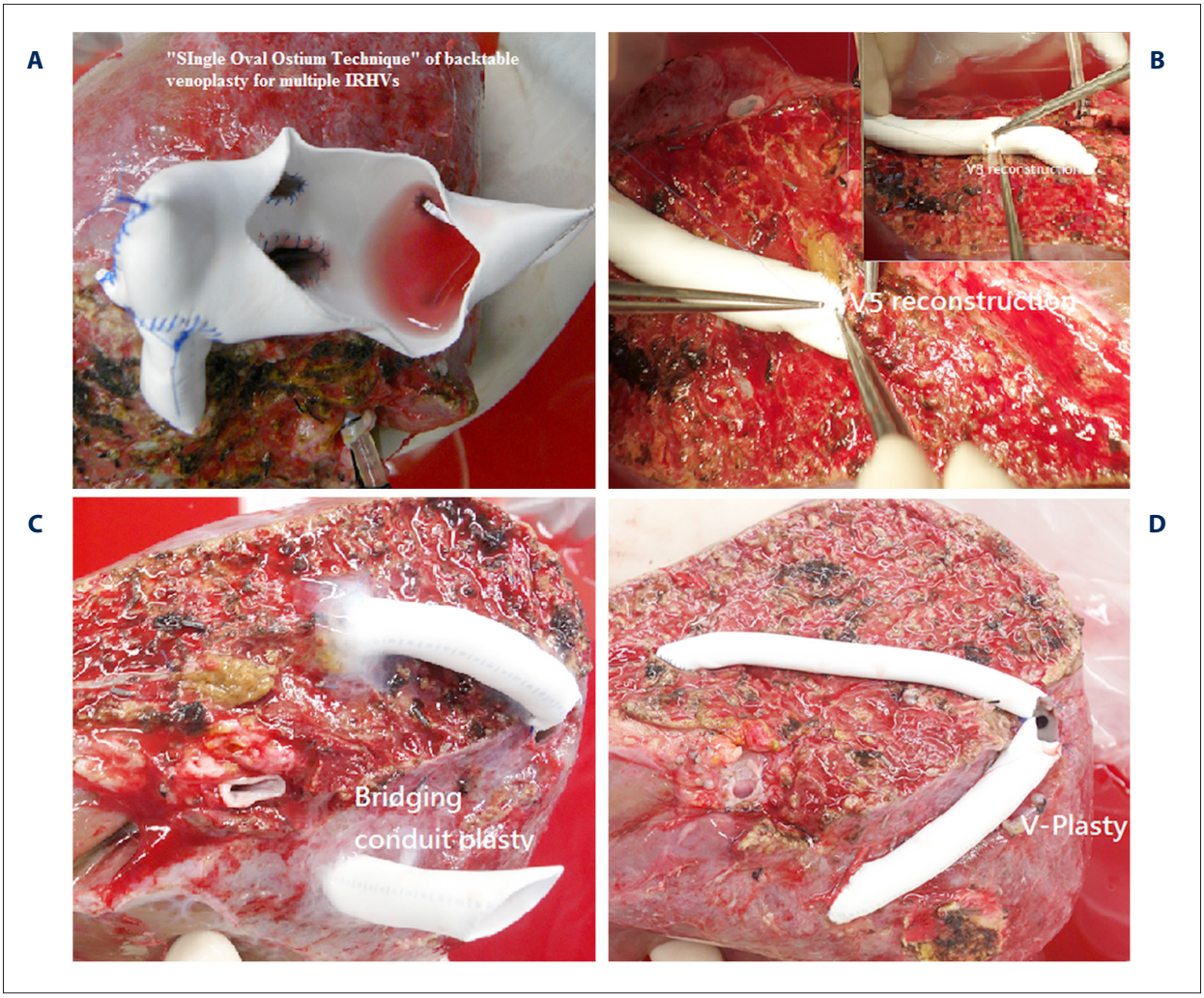

Figure 1. (**A**) "Single oval ostium technique" for backtable venoplasty of anomalous IRHVs [9]. (**B**) Backtable reconstruction of MHV tributaries. (**C**) 'Bridging conduit plasty' to reconstruct MHV tributaries and IRHV [10]. (**D**) "V-Plasty" for combined MHV and IRHV reconstruction to form a common outflow channel [3].

duodenum, causing silent perforation without any evidence of peritonitis (Table 1 from serial number 2 to 4).

Patient 1 in this series developed ePTFE graft thrombosis and complete occlusion of the liver allograft outflow two years after the LDLT surgery (Figure 2). In this patient, the outflow reconstruction was done using the "single oval ostium" technique [9]. At 24 months post-transplantation, the patient was admitted to an emergency ward with signs of liver allograft outflow obstruction and septic shock. Subsequent imaging studies of the abdomen revealed thrombus formation of the ePTFE graft extending to the IVC. However, before any surgical management could be instituted, the patient died due to multiorgan dysfunction secondary to overwhelming sepsis.

Patient 2 presented with intermittent high fever and upper-gastrointestinal bleeding during the 7th post-transplant month. Upper-gastrointestinal endoscopic examination revealed graft protrusion into the second portion of the duodenum, with no active bleeding or signs of inflammation (Figure 3A). The abdominal examination was negative for peritonitis and no systemic evidence of sepsis was present. A subsequent abdominal CT scan confirmed the findings of ePTFE graft migration into the duodenum, along with thrombosis and pneumatic shadows inside the vascular graft (Figure 3B). An exploratory laparotomy was performed, which revealed an organized thrombus with total occlusion of the ePTFE graft (Figure 3C). The graft was surgically resected from the cut surface of the liver, without formal hepatectomy. The V5 and V8 branches were found to be occluded, with no backbleeding at the site of their anastomosis with the graft. At the lower end of the ePTFE graft, there was an organized thrombus and the graft was resected just above its junction over the IVC. There was no evidence of bleeding at the lower end of the anastomotic

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Table 1. Characteristics of the LDLT recipients with ePTFE graft related complications.

	Patient 1	Patient 2	Patient 3	Patient 4
Gender/Age	Female/54 years	Female/67 years	Female/63 years	Male/22 years
Pre-Transplant diagnosis	HBV related HCC	HCV related ESLD	HCV related ESLD	Biliary atresia
MELD score	20	15	12	15
Type of backtable venoplasty	"Single Oval Ostium" technique [9]	MHV reconstruction using ePTFE graft	"Bridging Conduit Plasty" using two ePTFE graft [10]	"V-Plasty" technique of outflow reconstruction using dual ePTFE grafts [3]
Post-transplant complication	ePTFE graft thrombosis with complete occlusion and sepsis	ePTFE graft migration into second portion of duodenum with infection	Splenic artery pseudoaneurysm rupture ePTFE graft migration into second portion of duodenum with infection	ePTFE graft migration into second portion of duodenum with intra-abdominal infection
Interval between LT and detection of the complication	24 months	13 months	12 months	5 months
Presenting symptoms	Fever with signs of septic shock	Fever, Upper gastro-intestinal bleeding	Fever	Fever
Graft patency	Total occlusion	Total occlusion	Partial occlusion	Total occlusion
Outcome	Expired	Recovered well and alive	Expired after 1 month	Recovered well and alive

MELD – model for end-stage liver disease; LT – liver transplantation; ESLD – end-stage liver disease; HCC – hepatocellular carcinoma.

site with the IVC due to organized thrombus. However, there was no extension of the thrombus into the IVC. The duodenal perforation site was closed in layers (Figure 3D). The patient received broad-spectrum antibiotics along with standard immunosuppressive regimen as described before [11]. The patient was discharged on the 21st day after admission, with stable liver functions.

For Patient 3, the outflow reconstruction of the right liver allograft was done using "bridging conduit plasty" to reconstruct the MHV and the IRHVs [10]. Protocol splenectomy was performed during LDLT due to underlying hepatitis C viral infection status. She developed hemoperitoneum due to splenic arterial stump rupture in the 5th postoperative month, for which an exploratory laparotomy was performed to control the intra-abdominal bleeding after an emergency transarterial embolization of the splenic artery (Figure 4A). However, after 12 months of LDLT, the patient developed persistent high-grade fever and a CT scan of abdomen was performed to exclude any possible abdominal source of infection. Thrombotic occlusion of the ePTFE graft and its migration into the second portion of the duodenum were noted, without any signs of peritonitis (Figure 4B, 4C). Emergency laparotomy was done to remove the ePTFE graft that was perforated into the duodenum. Its junction with the IVC was closed in layers with 6-0 Prolene sutures. The second limb of the ePTFE graft, although thrombosed, could not be removed due to severe adhesions to the liver parenchyma and the IVC (Figure 4D). As it was not adhered to the adjacent viscera, it was left *in situ*. The perforation of the duodenum was closed in layers by standard technique. After re-exploration surgery, the patient was treated in the ward and received broad-spectrum antibiotics. However, the patient continued to have low-grade postoperative fever and her clinical condition deteriorated in the 3rd post-operative week. One month after the exploratory laparotomy, the patient expired due to uncontrolled sepsis leading to multi-organ failure.

Patient 4 in this series underwent LDLT for biliary atresia at the age of 22 years. Outflow reconstruction in this patient was done by "V-Plasty" technique, which combined the MHV and the IRHVs into a common orifice using dual ePTFE vascular grafts [3]. The patient had high-grade fever and upper-abdominal pain in the 5th post-transplant month, for which a CT scan of the abdomen was done to rule out the ePTFE graft as a potential source of infection. The imaging study revealed thrombosis of the MHV reconstructed portion of the ePTFE graft, which was found to be perforated into the second portion of

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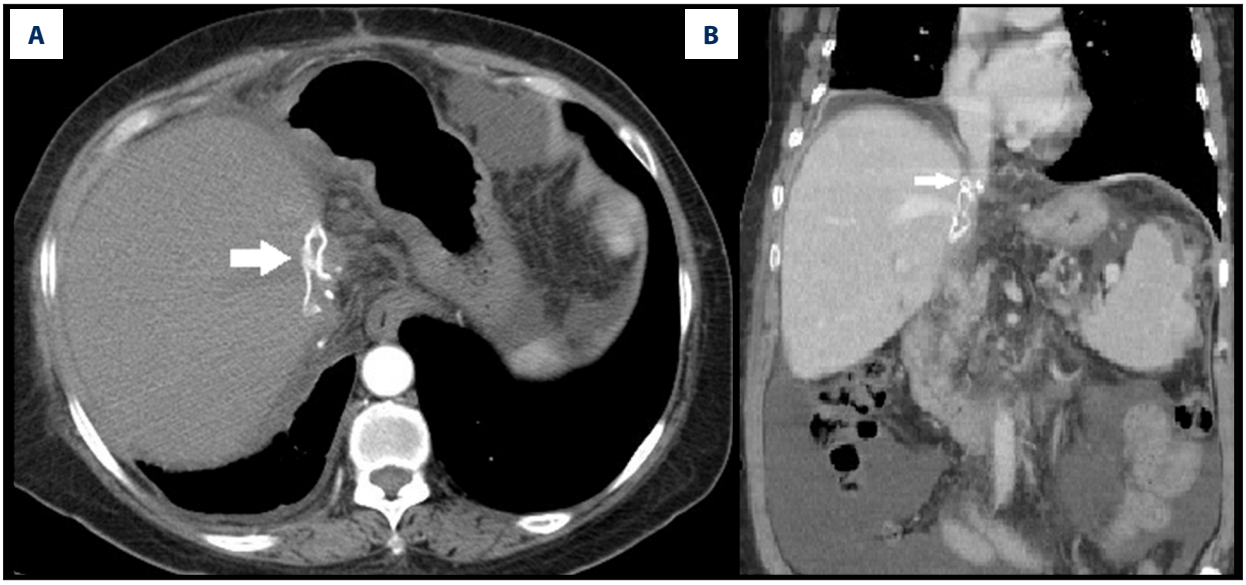

Figure 2. (**A, B**) Shows the CT scan abdomen images of ePTFE graft thrombus extending to the IVC. The white arrows in both images show the site of thrombosis causing complete occlusion.

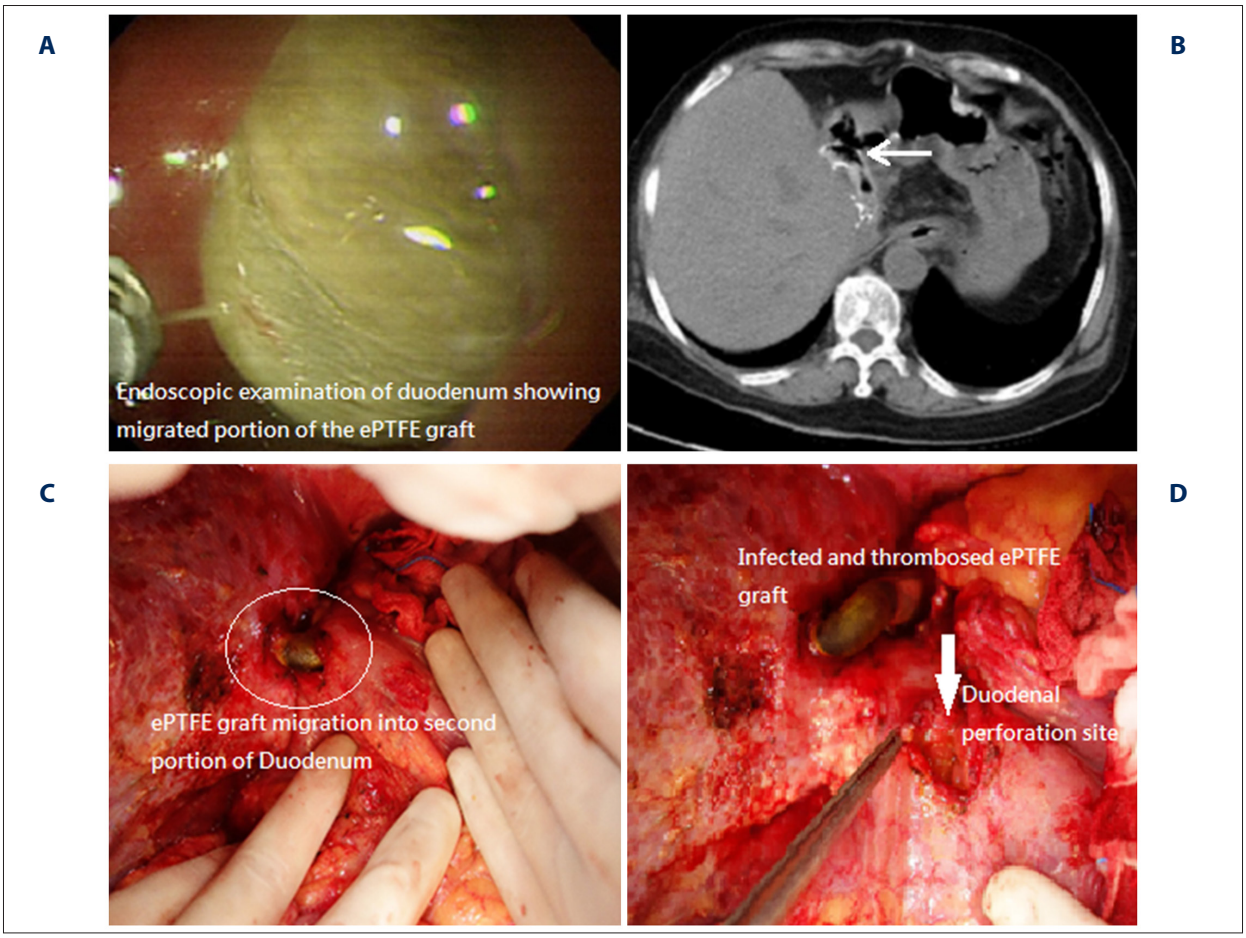

Figure 3. (**A**) Endoscopic examination of duodenum showing migrated portion of the ePTFE graft. (**B**) CT scan abdomen showing the migration of the ePTFE graft in the second portion of the duodenum with pneumatic shadows within (white arrow). (**C, D**) Intraoperative images showing the migrated graft and perforation in the second portion of the duodenum.

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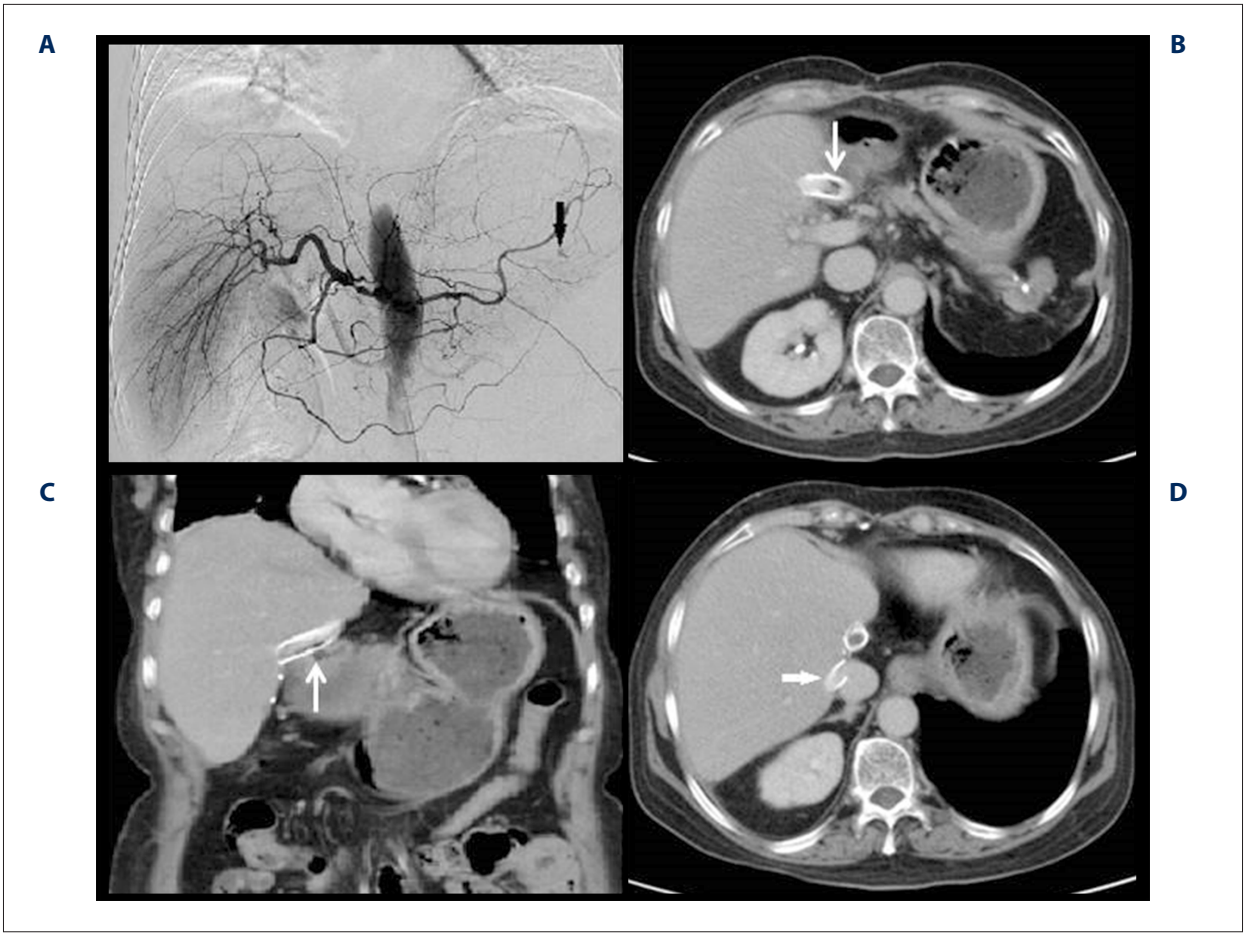

Figure 4. (**A**) Splenic arterial angiography showing extravasation of contrast (black arrow pointing the site of extravasation). (**B, C**) CT scan images of migrated of a ePTFE graft into the duodenum. (**D**) CT scan image showing thrombotic occlusion of the second limb of the ePTFE graft (white arrow).

the duodenum, with no findings suggestive of overt or localized peritonitis (Figure 5). Exploratory laparotomy was performed to remove the thrombosed ePTFE graft, and the duodenal perforation was repaired. Another limb of the ePTFE graft draining the IRHVs was patent and appeared healthy; therefore, it was not removed. During the first week after re-exploration, the patient developed a duodenal leak, for which a percutaneous duodenostomy tube was inserted under CT guidance. The patient recovered well and was discharged with a duodenostomy tube in place. The laboratory values for the liver function were within normal limits. The duodenostomy tube was removed during the 2nd postoperative month, without any complications.

Our experiences with ePTFE graft migration led us to start using omental packing between the liver allograft raw surface bearing the ePTFE graft and the adjacent hollow viscous organs just prior to closure of the abdomen (Figure 6). This maneuver helps prevent adhesions between the synthetic graft and the adjacent viscera.

Microbial study

Microbial study for blood and ePTFE graft culture showed mixed growth of microbes, including coagulase-negative staphylococci, gram-negative bacilli, *Pseudomonas aeruginosa*, *Lactobacilli*, *Klebsiella pneumoniae,* and *Candida albicans*. *Staphylococci aureus* was the most common microbial organism causing infection among all the patients. Patients 1 and 2 of this cohort had superadded fungal infection by *Candida albicans*. In patient 3, *Lactobacillus* bacteremia was additional source of septicemia.

Discussion

The right liver allograft is a partial graft and requires reconstruction of the venous tributaries to restore the anterior sector venous drainage if MHV is not included and/or in presence of multiple inferior right hepatic veins. The ePTFE synthetic grafts are commonly used interpositional conduits during the backtable venoplasty procedure of such liver allografts, with excellent short- and

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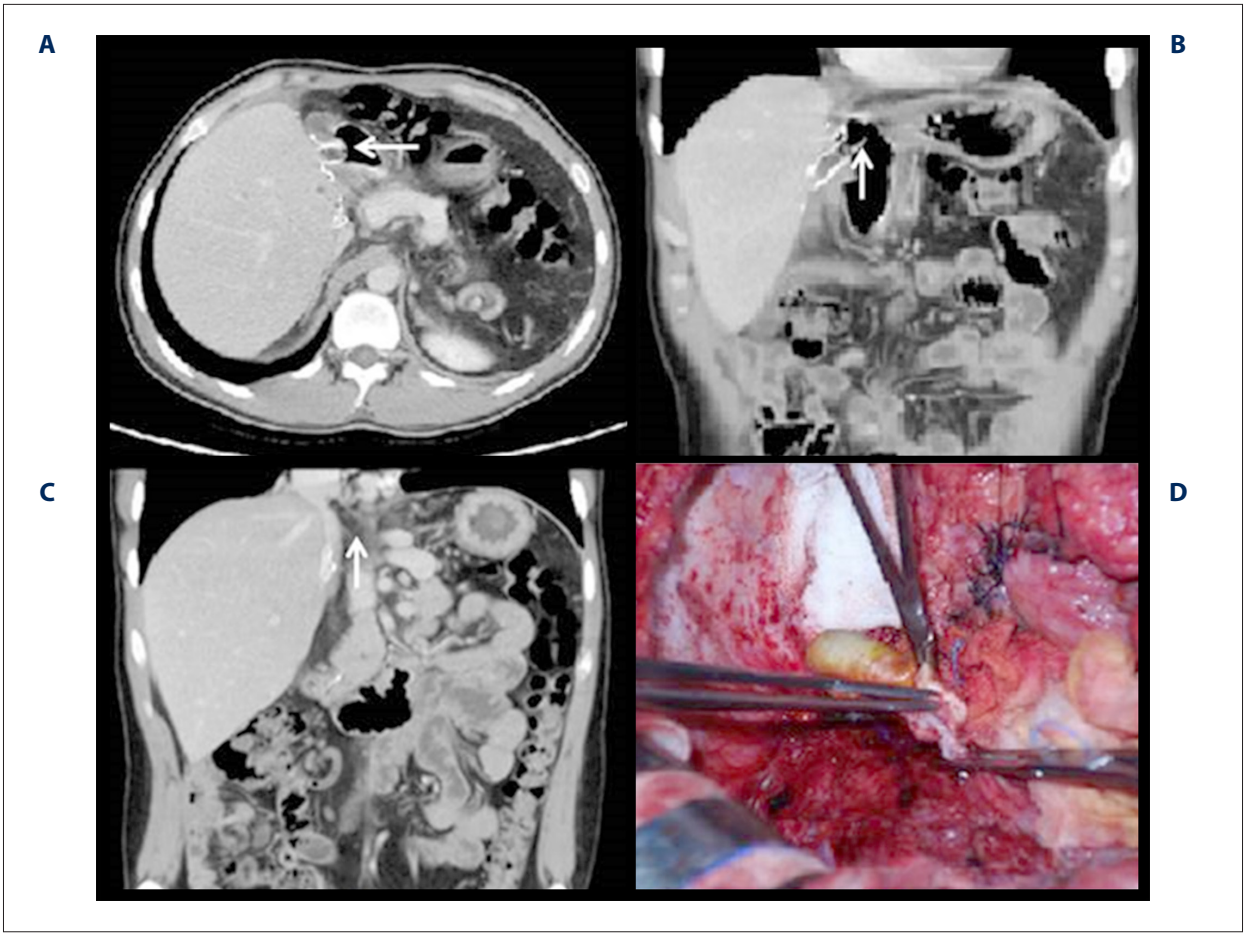

Figure 5. (**A–C**) CT scan images showing migrated ePTFE graft into the second portion of the duodenum. (**D**) Surgical removal of the ePTFE vascular graft.

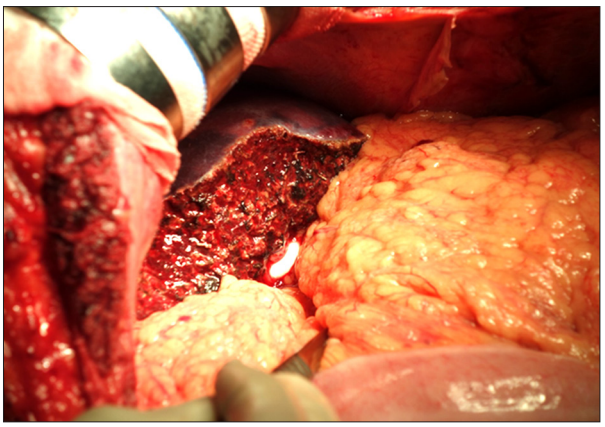

Figure 6. Omental packing between the cut surface of the liver allograft and hollow viscous organs to prevent adhesions.

long-term graft outcomes [2,3,8]. Thrombosis of the graft and possible risk of infections, although rare, are the possible complications of ePTFE use in LDLT recipients. Also, liver transplant recipients with Child C status and postoperative immunosuppression have an increased risk of infection. ePTFE graft migration into the surrounding hollow viscous organs causing perforation has been described recently, and tends to narrow the safety margin for the use of the ePTFE synthetic grafts [5–7]. However, such complications are fortunately rare and the safety and feasibility of ePTFE use in LDLT has been proven by several studies [2,3,8,10].

In our experience, the complication rate in LDLT recipients directly related to ePTFE vascular grafts was 1.52% (4/262). The graft migration occurred in 1.1% of the LDLT recipients (3/262) after LDLT, with a mortality rate of 0.4%. Although this rare set of complications does not narrow the safety profile of ePTFE use, in the absence of timely diagnosis and immediate surgical intervention it can lead to potentially fatal complication such as sepsis secondary to intestinal perforation. In this case series, the dense intestinal adhesions and multiple abdominal surgeries were the important risk factors. We hypothesize that the acute thrombotic occlusion of the ePTFE vascular graft increases the perigraft inflammation, which is worsened by the superadded microbial infection, should it occur. This process increases the process of adhesion of the ePTFE graft to adjacent organs, such as the stomach, duodenum, or extrahepatic bile duct, which can

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potentiate vascular graft migration. Two patients in our study cohort were subjected to splenectomy, while the remaining 2 patients had multiple abdominal surgeries. There were 3 conspicuous findings of the graft migration in these patients. First, the duodenum was the most common site of the migration, and the perforation was silent without any evidence of peritonitis. Second, there was no liver allograft dysfunction with normal liver enzymes, despite ePTFE graft thrombosis. Third, surgical intervention was necessary to remove the infected graft, which was proven to be an adequate treatment without need for formal hepatectomy. As mentioned in our previous studies [3,8], the intrahepatic venous collateral channels are expected to develop within 2 months after liver transplantation, and the patency of the ePTFE graft does not serve the same purpose after two months post-transplantation. Hence, its removal after this period has no effect on liver allograft venous outflow. However, acute thrombosis of the ePTFE vascular graft leading to complete obstruction in the immediate postoperative period can harm liver allograft function, which can increase mortality and morbidity.

Infection of the ePTFE graft is a feared complication that may cause rapid deterioration of the patient's clinical condition without prompt medical treatment for underlying infection. The ePTFE graft has a characteristic node-fibril lattice structure with an average pore size (inter-nodal distance) of 30 μm for a standard graft, which is believed to affect the rate of development of the neointima and endothelialization, which protect against infection [12]. The portion of the graft that migrated into the intestine allows formation of biofilm by the intestinal microbes, and this has been assessed by quantitative cultures and microscopy techniques [13]. This process can lead to translocation of intestinal microorganisms across the migrated portion of the ePTFE graft and can exacerbate the infection. The thrombosis and graft infection probably increases the ePTFE graft wall permeability, leading to the systemic spread of intestinal microorganisms and resulting in sepsis. Timely blood cultures can help in identifying potential pathogens, which helps narrow the antibiotic spectrum. The infection sources in the present case series were both bacterial and fungal. Coagulase-negative staphylococci and *Candida albicans* were revealed by blood culture studies to be the potential pathogens causing septicemia. All 3 patients with graft migration presented with high-grade fever, and 1 patient additionally had an episode of upper-gastrointestinal bleeding. In the presence of synthetic vascular grafts, any sudden high-grade fever should be investigated for possible liver allograft origin. If the infection source is removed, the potential complications can be averted. Hence, ideal management in such situations is to remove the infected ePTFE graft, which does not necessarily need a partial hepatectomy, bearing the ePTFE graft along with broad-spectrum antibiotics to control the sepsis.

In patient 3 of this series, the second ePTFE graft was not the cause of perforation, but was found to be thrombosed. The ePTFE graft was severely adhered to the liver, which would require a partial hepatectomy. Hence, the vascular graft was undisturbed and left *in situ*. However, the patient developed multiorgan failure secondary to *Lactobacillus* septicemia. *Lactobacillus* septicemia is a rare clinical entity and its presence in potentially sterile fields should be regarded as an alarming finding [14]. We believe that the thrombosed graft acted as the source for constant infection in this patient. In such a case scenario, it is ideal to surgically remove the infected vascular graft along with the rim of the liver parenchyma bearing the tightly adhered ePTFE graft. Omental packing between the intestine and the raw surface of the liver allograft bearing the ePTFE graft before closing the abdomen can prevent direct contact with the ePTFE graft and stomach or duodenum. Complete obstruction of the graft with subsequent septicemia, although rare, occurred in 1 patient (0.38%). The imaging studies of this patient showed complete outflow obstruction due to ePTFE graft thrombosis. In this patient, the right liver allograft had venous anomalies with multiple IRHVs.

As per our protocol, we consider the patency rates of ePTFE vascular grafts during the first 2 months after LDLT as crucial for liver allograft regeneration and liver allograft function. The patency of the graft vessels beyond this period does not affect liver function due to the well-developed intrahepatic venous collateral channels, which further reduce blood flow in the vascular conduits. This results in chronic clogging and thrombotic silent occlusion of the vascular conduit [3,10].

Conclusions

Thus, with a low overall complication rate of 1.52%, the use of ePTFE vascular grafts in LDLT still can be considered as safe and feasible. However, despite of the large safety margin, the rare complications directly related to ePTFE vascular grafts in LDLT raise concerns among the centers where cryopreserved vessels are rarely available. The migration of the ePTFE grafts in the duodenum was noticed 1.1% of the recipients who received liver allografts with ePTFE vascular conduits. This clearly increases the risk of mortality due to impending perforation and subsequent risk of sepsis. However, timely surgical intervention to remove the infected vascular graft is effective. Also, microbial study helps to understand the pattern and source of infective microbes, which helps in directing broad-spectrum antibiotic therapy. Omental packing between the raw surface of the liver graft and surrounding the hollow viscous organs helps to prevent direct contact of the ePTFE grafts with the stomach and duodenum.

Conflicts of interest

None.

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