Multidrug-Resistant Bacterial Sepsis and Inferior Vena Cava Thrombosis in Liver Transplant Recipients Used Synthetic Vascular Graft: Three Fatal Cases

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ABSTRACT

Synthetic vascular grafts are commonly used in liver transplantation. Thrombosis is a possible complication of using expanded polytetrafluoroethylene (e-PTFE) grafts. Herein, we report on 3 cases of liver recipients who died of intermittent sepsis episodes emerged concurrently with the thrombosis in synthetic vascular grafts and inferior vena cava (IVC) vein. Right lobe liver transplantation from living donors was performed for 3 patients by using e-PTFE grafts between the liver and IVC. Although heparin had been administered, thrombosis was developed in vascular graft and IVC extending to the right atrium; it was developed within 1–4 months of transplantations. All 3 patients suffered from recurrent sepsis episodes (4, 5, and 6 attacks for each patient) by different multidrug-resistant bacterial species. Treatment attempts including thrombolytic and antimicrobial drugs made, and surgical, endoscopic and radiological interventions could not resolve the clinical situation. The patients died of septic complications. We concluded that severe recurrent sepsis attacks may develop in liver transplant recipients when IVC and synthetic vascular graft were thrombosed. Removing the e-PTFE graft may be benefit for the treatment.

KEYWORDS: Synthetic graft; Liver transplantation; Venous thrombosis; Sepsis

INTRODUCTION

Liver transplantation (LT) is the treatment of choice for patients with end-stage liver disease. Living donor LT (LDLT) may be an option to overcome the organ shortage. However, rejection, infection, surgical complications are still the most important causes of morbidity and mortality after LT [1]. While biliary tract problems are more common among surgical complications, vascular problems are less frequent, leading to graft failure (53%) and mortality (33%). United Network for Organ Sharing reports that the incidence of thrombosis and stenosis in hepatic artery, portal vein, hepatic vein, and inferior vena cava (IVC) is from 3%–10% in adult patients [2].

Synthetic vascular grafts are commonly used for overcoming shortened or complex vascularity of right lobe liver graft in LDLT. Although the safety of expanded polytetrafluoroethylene (e-PTFE) synthetic vascular grafts in LDLT has been proven, complications such as graft thrombosis and infection may be serious conditions [3]. The most common infections in the early period after LT (within first 30 days) are related to surgical and/or vascular problems. Linares, *et al*, report that the sepsis episodes due to multi-drug resistant (MDR) bacteria pose a high risk for mortality in liver transplant recipients, particularly in those with underlying surgical problems [4].

Herein, we present three patients with right lobe LDLT in our institute, who developed

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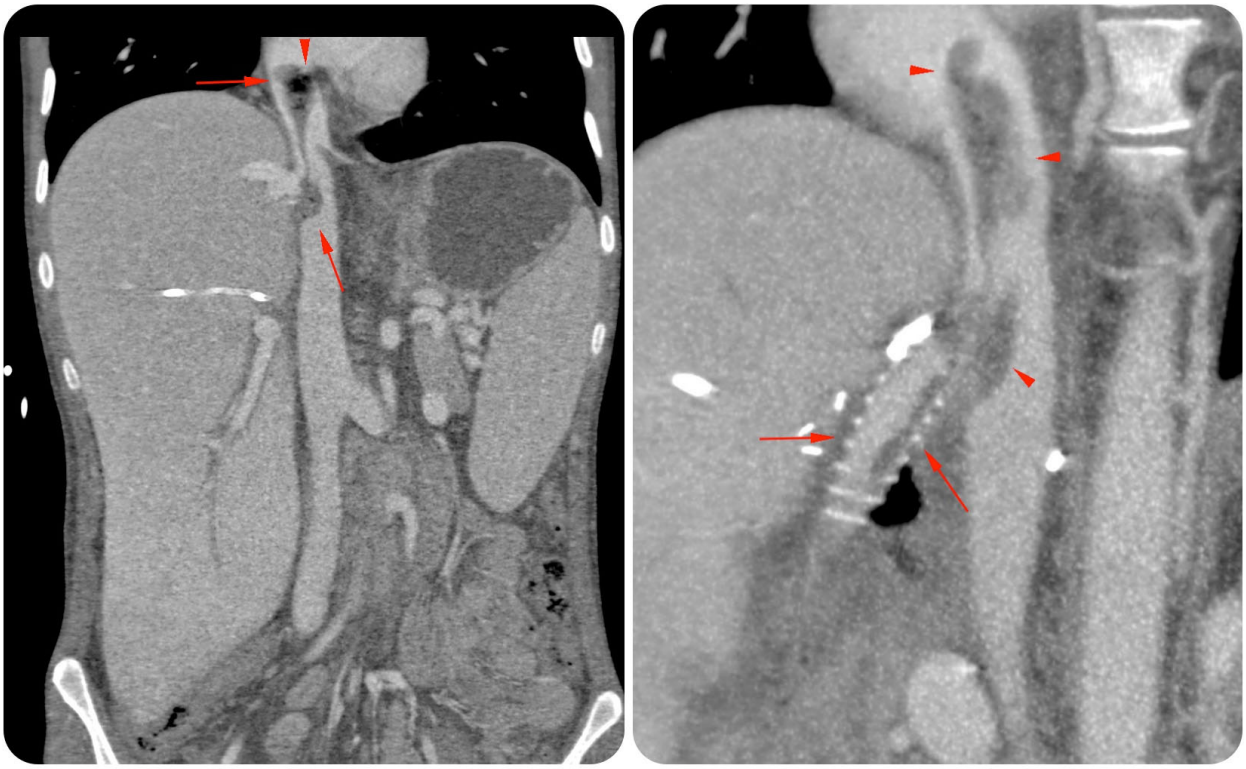


Figure 1: Coronal MIP CT image showing hypodense thrombus material (arrows) extending from the IVC to atrio-caval junction and air density (arrowhead) in the thrombus are observed (A). Thrombus material (arrowheads) extending through PTFE graft (arrows) to IVC seen on the volume-rendered CT image (B)

recurrent sepsis attacks with thrombosis in e-PTFE vascular grafts and IVC within the first and fourth month of LT.

CASE 1

A 33-year-old man with end-stage liver disease (MELD and Child-Pugh scores of 23 and 10, respectively) underwent LDLT. The patient had four hospital admissions, staying 23 days in the ICU and hospitalized for a total of 79 days post-LT. Invasive procedures such as two percutaneous abscess drainage, three endoscopic retrograde cholangiopancreatographies (ERCP), two percutaneous transhepatic cholangiography (PTC), and two catheter revision were performed at different times. Thrombosis was first detected on MDCT in IVC on post-operative day 104; transluminal angioplasty where the thrombus was partially aspirated following insertion of the IVC filter, was performed on day 105 post-transplantation (Fig 1). Six sepsis episodes occurred in the patient—one secondary to bilioma on day 24, two episodes secondary to pneumonia on days 64 and 79, and three intra-abdominal sepsis episodes on day 104 after detection of thrombosis. Despite appropriate antibiotic therapy, he died of sepsis on day 132 post-LT.

CASE 2

A 51-year-old woman was followed for the last five years with cryptogenic chronic liver failure. She was referred to our institute for LT. The patient had type II diabetes mellitus for the last three years and Parkinson's disease for five years. The MELD and Child-Pugh scores on admission were 23 and 12, respectively. On the post-operative day 2, the patient was re-operated for hepatic artery repair for hemorrhage. The patient had three hospital admissions—90 days in the ICU and 57 days in the clinic after LT. Three percutaneous abscess drainage, two ERCPs, one PTC, and three catheter revisions were performed on differ-

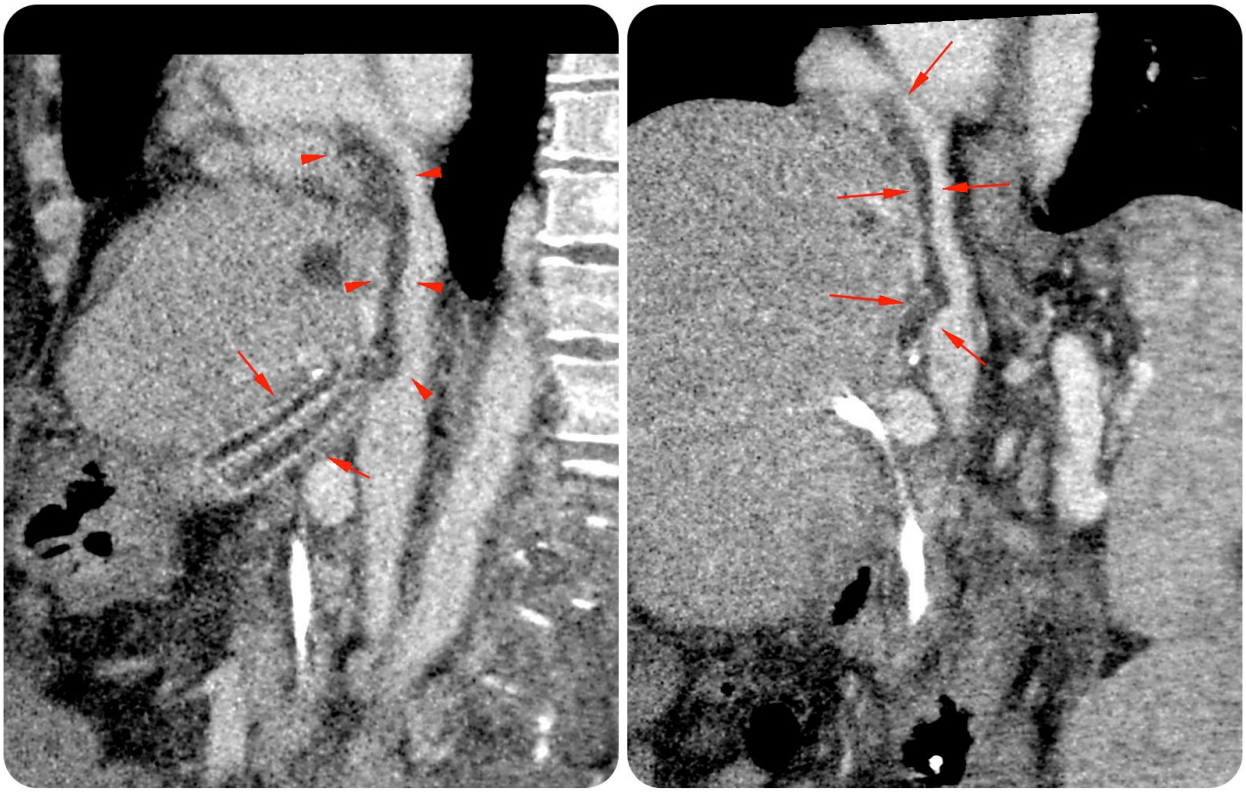


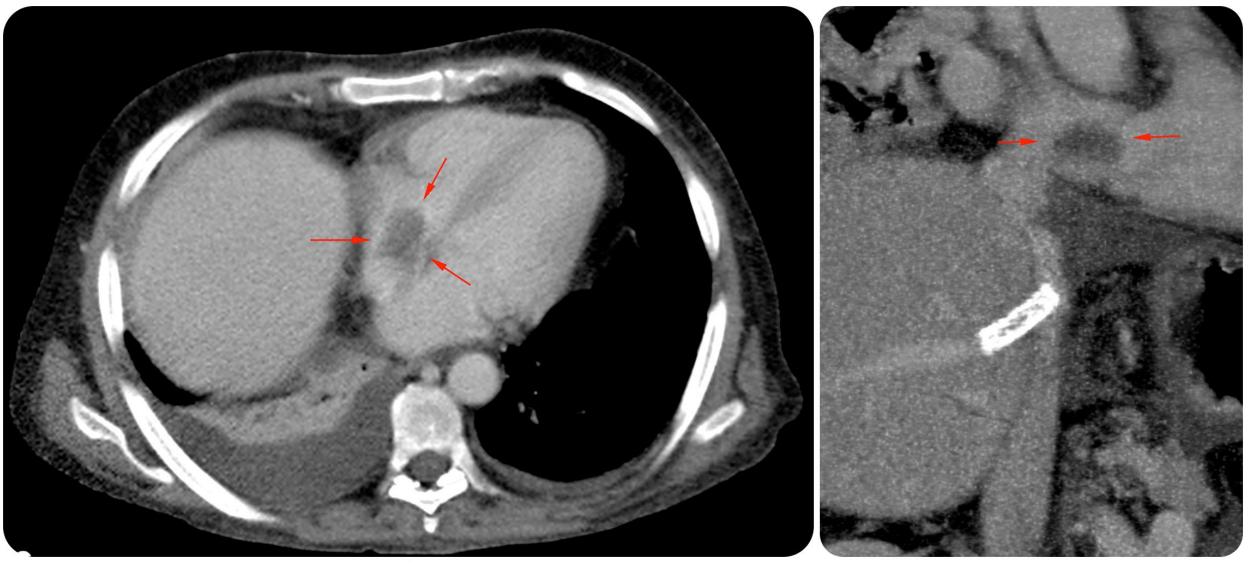
Figure 2: Hypodense thrombus material (arrowheads) in PTFE extension graft (arrows) and its extension into IVC and atrio-caval junction seen in the oblique coronal MPR MSCT images (A and B)

ent times; transluminal embolectomy was performed on post-operative day 65. Empirical antibiotic therapy was initiated for the patient who developed septic symptoms on the post-operative day 70. The thrombus was detected in IVC on MSCT at post-operative day 19 (Fig 2). Four sepsis episodes were developed after detection of thrombosis. She died of septic complications on day 186.

CASE 3

A 48-year-old man was followed with chronic hepatitis B for the last three years. He was referred to our institute for LT after being diagnosed with hepatocellular carcinoma (HCC). The patient had no comorbid conditions. The MELD and Child-Pugh scores on admission were 25 and 13, respectively. He received a living donor LT within Milan criteria. The patient had five hospital admissions—26 days in the ICU and 204 days in the clinic after LT. Thrombosis was first detected on the post-operative day 114 (Fig 3). The patient underwent transluminal angioplasty on the post-operative day 121 and intracardiac mass excision (cardiotomy, explorative cardiopulmonary bypass) on the 257th day post-LT. The pathology report of the mass excised from the right atrium revealed that it was infected thrombus material containing micro-organisms with bacillary appearance (Tables 1-3). The culture resulted in Klebsiella pneumoniae susceptible only to tetracycline. Two percutaneous abscess drainages, six times ERCP, four times PTC, two cholangiograms, and two catheter revision procedures were performed at different times. The first sepsis episode of the patient was secondary to pneumonia on the 30th day after LT. He died on the 278th day.

All the patients received the standard immunosuppression protocol (tacrolimus + mycophenolate mofetil + prednisolone). Immunosuppression continued with only tacrolimus and low-dose steroid at the end of the first month. On the 7th day, trimethoprim/sulfa-



A B

Figure 3: Hypodense thrombus (arrows) seen in the right atrium in the axial (A) and coronal MPR (B) CT images

methoxazole (80/400 mg, po, for 6 months) and valganciclovir (900 mg/day, po, for 100 days) were initiated for antimicrobial prophylaxis. Cases who were implanted synthetic vascular graft were given intravenous heparin after admission to the ICU after LT. Heparin infusion dose was individualized to provide an aPTT level of at least 1.5 times the baseline level and continued with warfarin. As soon as oral intake started, and if there was no hemorrhage risk, 100 mg/day acetyl-salicylic acid was also added.

Blood cultures were performed for all patients on BacT/ALERT 3D (BioMérieux, France) automatized blood culture system, and bacterial identifications were done with Vitek-2 (BioMérieux, France) bacterial identification system. Sepsis diagnosis was established according to the International Guidelines for the Management of Sepsis and Septic Shock criteria [5].

DISCUSSION

Biliary complications such as biliary stenosis, bile leakage, and sphincter of Oddi dysfunction, can cause allograft dysfunction, retransplantation, and even death. With an incidence of 5.8%–24.5%, these occur more frequently in adults in the first three months of LT and account for 10%–35% of morbidity and 2%–7% of mortality [6]. In most cases, endoscopic and radiological interventions are effective; surgical approach is mandatory and safe in selected cases.

The second most common complication develops in the vascular system. While hepatic artery and portal vein stenosis and thrombosis are more frequent, intrahepatic and suprahepatic vena cava stenosis are less common [7]. Early anticoagulation is required to prevent recurrence of Budd-Chiari syndrome with thrombosis of the IVC. Anticoagulation should be initiated with heparin and continued with warfarin. In a study conducted by Kienlein, *et al*, it was emphasized that techni-

Table 1: Sepsis episodes and the isolated micro-organisms

Parameters	Case 1	Case 2	Case 3
Number of sepsis episodes	6	5	4
Dates of sepsis episodes (post-operative day)	24, 64, 79, 106, 117, 129	7, 62, 90, 124, 180	39, 126, 138, 252

Table 2: Blood culture and antibiotic susceptibility test results during sepsis episodes

Sepsis	Case 1	Case 2	Case 3
Episode 1	*P. luteola* (2) Colistin and Sefaperazon/Sulbactam sensitive, Gentamycin intermediate sensitive	*A. baumannii* (6) Colistin, Amikacin and Gentamycin sensitive	*E. coli* (3) Ceftazidime, Cefoxitin, Tigecycline, Meropenem and Imipenem sensitive
Episode 2	*P. aeruginosae* (2) Colistin, Amikacin, Gentamycin, Ciprofloxacin and Piperacillin/Tazobactam sensitive	*ESBL* (+) *E. coli* (4) Colistin, Amikacin, Gentamycin, Cefoxitin, Meropenem, Imipenemsensitive	*A. baumannii* (1) Colistin and Amikacin sensitive
Episode 3	*A. baumannii* (1) Colistin, Gentamycin and Levofloxacin sensitive	*E. faecium* (3) Vancomycin, Teicoplanin and Linezolid sensitive, Ampicillin resistant	*K. pneumoniae* (2) Colistin and Tetracycline sensitive
Episode 4	*ESBL* (+) *Klebsiella spp* (1) Colistin, Amikacin, Gentamycin, Cefoxitin, Meropenem, Imipenem sensitive	*IBL* (+) *Enterobacter spp* (1) Cefepime, Amikacin, Ceftazidime, Cefoxitin, Meropenem, Imipenem sensitive	*K. pneumoniae* (8) Panresistant
Episode 5	*P. aeruginosae* (5) Colistin, Amikacin, Gentamycin, Netilmicin and Ciprofloxacin sensitive	*A. baumannii* (2) Colistin and Amikacin sensitive, Sefaperazon/Sulbactam intermediate sensitive	
Episode 6	*E. faecium* (2), *Enterococcus spp* (1) Vancomycin, Teicoplanin and Linezolid sensitive, Ampicillin resistant		

cal complications such as bile leakage, biliary drain complications, and papillary stenosis would be developed in 6%–37.5% of patients even if the best standards are provided [8].

Here, we should ask ourselves about the basis of biliary complications—did recurrent sepsis episodes cause venous thrombosis? or did venous thrombosis trigger the sepsis episodes? A thrombus in the venous system can cause slowing blood flow, or even complete stasis that may provide an environment for colonization of and infection by micro-organisms. Thrombosis and possible risk of infections, although rare, are possible complications of e-PTFE used in LDLT recipients. The thrombosis and graft infection probably increased the e-PTFE graft wall permeability, leading to systemic spread of intestinal micro-organisms and resulting in sepsis. However, timely surgical intervention to remove the infected vascular graft is effective. Also, microbiological studies help to understand the pattern and source of infections, which helps in directing broad-spectrum antibiotic therapy [9]. Therefore, with a low overall complication rate of 1.52%, the use of e-PTFE vascular grafts in LDLT can still be considered safe and feasible [10]. In a study conducted by Yan, *et al*, 3 out of 24 LDLT recipients developed an infection (subphrenic abscess, pneumonia, and MODS) [11]. In another study conducted by Tuzuner, *et al*, 5 of 39 patients died of sepsis [12]. Therefore, it is not always easy to provide a clear answer to these questions.

We believe that the thrombosed graft could act as a source for recurrent sepsis attacks in these patients. This clearly increases the risk of mortality. In the three cases presented, possible causes of IVC thrombosis may be related to the use of e-PTFE grafts, moderate-grade malposition, surgical sutures, and/or a number of unpreventable factors. Donors were discharged on post-operative days 8, 10, and 11, respectively. None of these sepsis episodes were donor-induced. It is possible that the presence of biliary tract problems in the LT recipients, especially in the first 30 days, frequent radiological and endoscopic invasive procedures,

Table 3: Antibiotic therapy and treatment durations during sepsis episodes

Sepsis	Case 1	Case 2	Case 3
Episode 1	Colistin 14 days	Meropenem 17 days + Tigecycline 17 days	Meropenem 14 days
Episode 2	Piperacillin/Tazobactam 14 days	Imipenem/Cilastatin 14 days	Colistin+Sulbactam+ Tigecycline 21 days
Episode 3	Ceftazidime+Sulbactam+Tigecycline 14 days	Linezolid 14 days	Colistin+Meropenem 14 days
Episode 4	Meropenem 14 days	Imipenem/Cilastatin 14 days+ Amikacin 10 days	Colistin+Meropenem+ Tigecycline, ex 19th
Episode 5	Colistin 14+Amikacin 7 days	Cefaperazone/Sulbactam 14 days+ Amikacin 7 days, Colistin+Sulbactam, ex 7th	
Episode 6	Linezolid, ex 4th		

intensive immunosuppressive treatments, long hospitalization, and recurrent sepsis episodes may have a negative contribution to thrombus development in the caval system. Existing bile leakage can lead to resistant infections and bacteremia by bacteria passing through the pores of this synthetic thrombosed vascular grafts. Graft failure does not occur because the graft is sufficiently drained from other hepatic veins [13]. So, if we had removed the thrombosed e-PTFE grafts following the first sepsis attack, recurrent sepsis episodes would have been prevented.

In conclusion, even if the underlying main problem, such as bile leakage, is resolved with percutaneous or endoscopic procedures, recurrent sepsis episodes can occur when thrombosis develops in the caval system in LDLT recipients in whom synthetic grafts are used. The treatment may fail and results in mortality even if appropriate antibiotic combinations are given.

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