Transpl Int (1999) 12: 273–277

ORIGINAL ARTICLE

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Successful recanalization of late portal vein thrombosis after liver transplantation using systemic low-dose recombinant tissue plasminogen activator

Received: 4 May 1998
Received after revision: 16 March 1999
Accepted: 9 April 1999

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Abstract Portal vein thrombosis (PVT) is an infrequent complication following hepatic transplantation. However, deterioration of liver function and accompanying complications may be life threatening. Several attempts of surgical or percutaneous transhepatic procedures have been described. In some cases high dose fibrinolytic regimens have been successful. We describe the case of a male liver recipient with recurrent liver fibrosis due to hepatitis B reinfection and late portal vein thrombosis 45 months after transplantation. Complete recanalization was achieved using systemic low dose recombinant tissue plasminogen activator (rt-PA).

Key words Liver transplantation · Hepatitis B reinfection · Portal vein thrombosis · Recombinant tissue plasminogen activator lysis

Introduction

Portal vein thrombosis after orthotopic liver transplantation (OLT) is a rare event and occurs usually in the early postoperative period. Only few cases of late portal vein thrombosis after OLT have been reported up to now. Larger follow-up series after liver transplantation reported incidences of early or late PVT ranging between 1 and 2% [7, 9, 19]. We have experienced only two cases of PVT in 890 liver transplants in adult patients, as assessed by routine Doppler ultrasound examinations of all patients at least once a year.

Accompanying complications such as acute graft failure or bleeding of esophageal varices are often life threatening and require immediate reoperation or retransplantation [9, 20]. Small diameters of the portal

vein, preexisting PVT, surgical shunting procedures prior to OLT, or splenectomy are known risk factors for the development of PVT [9]. Depending on the extent of clinical deterioration, different attempts of treatment are feasible.

In otherwise asymptomatic patients, observation and possibly endoscopic treatment of esophageal varices seemed to be justified [2, 24]. For the management of acute esophageal bleeding or massive ascites, surgical shunting procedures or percutaneous transhepatic procedures have been suggested [6, 10, 13, 16].

We report the non-invasive management of late PVT, that occurred 45 months after OLT in a male patient with recurrent liver fibrosis due to chronic hepatitis B reinfection.

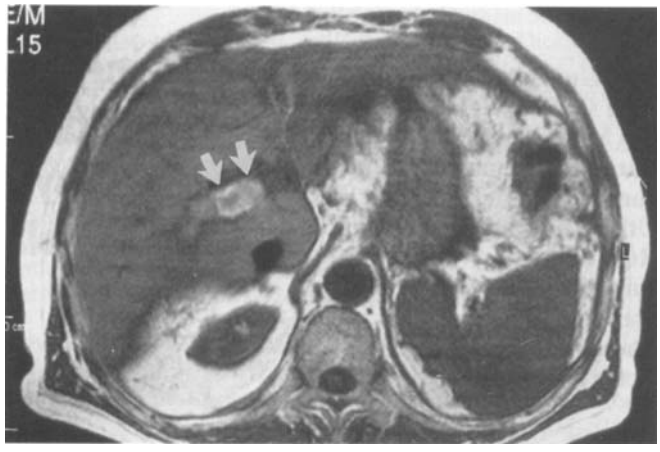

Fig. 1 Late portal vein thrombosis 45 months after liver transplantation: magnetic resonance imaging in axial sections demonstrates portal vein thrombosis with high signal intesity on T1-weighted images *(arrows)*

Case report

In January 1993, a 54-year-old male underwent OLT for chronic liver failure after a ten-year history of hepatitis B virus (HBV) infection. He had had no specific treatment prior to OLT. At the time of admission to our clinic, the patient suffered from ascites, esophageal varices, hepatic encephalopathy, hepatorenal syndrome, and hypersplenism (Child stage C). There was no evidence of PVT. The patient's history was otherwise unremarkable, apart from a cholecystectomy in 1970. Laboratory findings were positive for HBV-DNA at a low grade.

A suitable liver graft was transplanted in a standardized technique [12]. In addition, intraoperative banding of the splenic artery to a diameter of 2.5 mm to prevent lienalis-steal-syndrome was performed. Consequently, splenic volume gradually decreased from 700 ml to 550 ml two years after OLT and remained unchanged thereafter. Also, postoperative measurements of portal vein (17–25 cm/s) and hepatic artery (27–48 cm/s) flow were within the normal range until June 1996.

During the anhepatic phase 10,000 Units of anti-HBs hyperimmunoglobulin (HBIG, Hepatect®, Biotest, Dreieich, Germany) were administered, the cold ischemia time was 11 h. The immunosuppressive regimen was started as triple therapy, consisting of tacrolimus, prednisolone, and azathioprin. In addition, HBIG-immunoprophylaxis was continued until HBV reinfection in February 1994 (2,000 Units every 2 weeks).

The postoperative course was complicated by severe nephrotoxicity requiring hemodialysis. Furthermore, a severe neurotoxicity with stuporous states occurred. Both complications regressed under tacrolimus dose reduction. The patient was discharged from hospital 47 days post-OLT with compensated renal insufficiency (creatine 1.8 mg/dl, urea 65 mg/dl). During the first year, two episodes of acute rejection were confirmed by biopsy, both sensitive to steroid-bolus therapy, without evidence for HBV reinfection. Primary immunosuppression was changed to cyclosporine A, due to renal toxicity, and continued as triple therapy. Ultrasonic examinations after one year showed no evidence of PVT, and antibody values (anti-HBs) always exceeded 100 Units per ml. Antihypertensive treatment was necessary from August 1993 onwards.

In February 1994, 13 months after OLT, increased liver enzymes were detected, and percutaneous liver biopsy confirmed HBV reinfection. Laboratory findings were positive for HBsAg and HBV-DNA. Virostatic therapy with famciclovir was initiated at a dose of 500 mg twice daily. Two years after OLT under continued famciclovir therapy, the patient was still in good condition, and ultrasonic examinations showed no evidence for liver cirrhosis or PVT. Laboratory findings showed a slight increase of liver enzymes and known compensated renal insufficiency. HBsAg and HBV-DNA were still positive at low levels. Famciclovir was reduced to 500 mg daily due to renal toxicity. In January 1996, three years after OLT, routine liver biopsy showed a slight portal fibrosis, without any changes in laboratory findings. Ultrasound of the liver still remained normal (orthograde portal flow: 19 cm/s). In June 1996, first an ultrasonic examination in a referring hospital suggested a thrombus inside the portal vein, but flow measures were still positive at a decreased rate of 11 cm/s. In October 1996, the patient complained about intense upper abdominal pain and nausea, and considerable increased liver enzymes were detected in a referring hospital. Ultrasound Doppler technique confirmed PVT. Subsequently, the patient was transferred to our clinic.

At the time of admission, the patient presented with moderate upper abdominal pain and jaundice. Laboratory findings were as follows: creatine 3.1 mg/dl, urea 73 mg/dl, total bilirubin 1.7 mg/dl, ASAT 18 U/l, ALAT 11 U/l, γ-GT 46 U/l, alkaline phosphatase 227 U/l, GLDH 12.4 U/l. Ultrasonic examination and magnetic resonance tomography (MRT) confirmed PVT and thrombosis of the splenic and mesenteric veins (Fig. 1). Hepatic veins and hepatic artery were well perfused. There was no evidence of intra- or extrahepatic cholostasis, and endoscopy showed distinct esophageal varices and congestive gastritis without any evidence of acute bleeding.

Referring to reports on successful systemic rt-PA lysis in patients with venous occlusive disease after bone marrow transplantation [26] and the favorable administration access, we decided to perform systemic low dose rt-PA lysis. Twenty mg rt-PA (Actilyse®, Thomae, Biberach, Germany) were administered continuously at 0.25 mg/kg per day. In addition, the patient received 25,000 IU heparin per day to adjust the partial thromboplastin time at around 70 s. Other coagulation measurements including fibrinogen were not altered during the treatment. First, daily ultrasonic Doppler techniques showed a slight flow signal on day two of treatment, and MRT angiography on day five demonstrated a 50% recanalization of the portal vein.

On day ten, another MRT angiography confirmed successful complete recanalization of PVT (Fig. 2). Following complete recanalization, a portal flow at around 20 cm/s was re-established

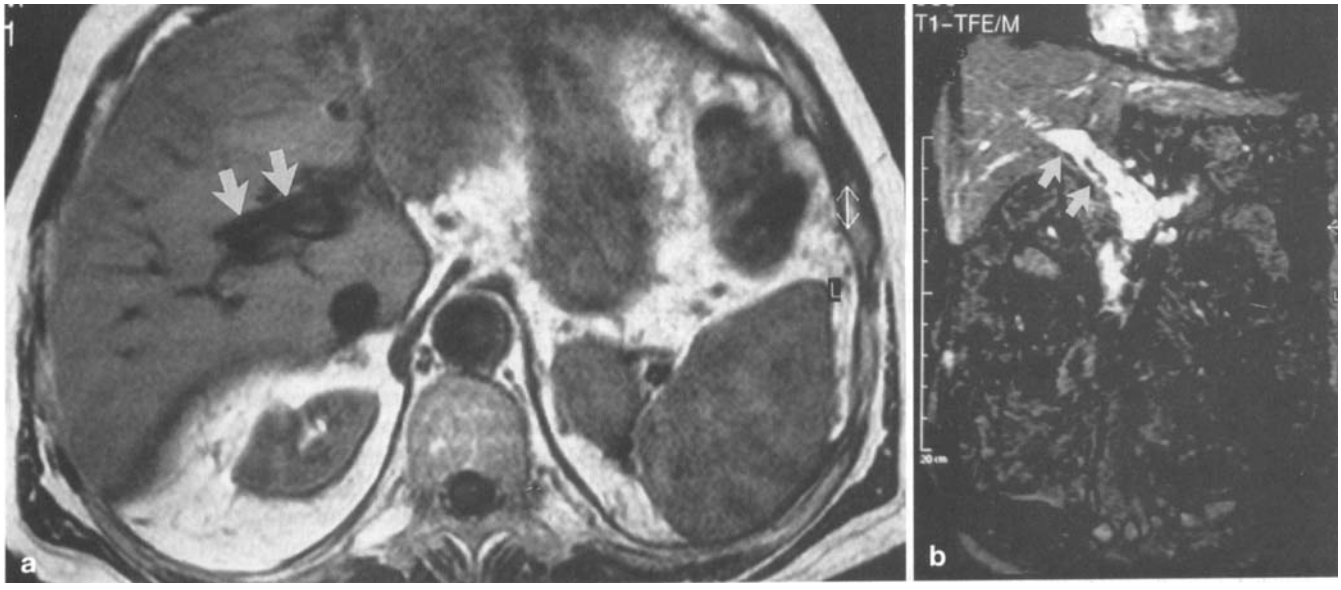

Fig. 2 Successful recanalization of portal vein thrombosis after a ten day course of low dose rt-PA: T1-weighted axial images **(a)** and coronal magnetic resonance angiography; **(b)** of the abdomen demonstrate recanalization of the portal vein with regular flow patterns *(arrows)*

and remained unchanged thereafter. We then discontinued rt-PA administration and started an effective anticoagulation with kumarin derivates. When discharged from hospital 21 days after admission, the patient presented nearly normal liver enzymes and known compensated renal insufficiency. The prothrombin time was adjusted at around 20%.

In November 1996, azathioprin was replaced by mycophenolat mofetil (0.5 g twice daily) due to another episode of increased liver enzymes without any evidence of PVT. Liver biopsy was not performed, because of anticoagulation treatment. Due to badly decreased renal function in March 1997, famciclovir was replaced by lamivudine 100 mg daily.

In November 1997, the patient presented in very good condition in our outpatient clinic. Renal function was stable and liver enzymes were within a normal range (creatine 3.4 mg/dl, urea 110 mg/dl, total bilirubin 0.5 mg/dl, ASAT 11 U/l, ALAT 18 U/l, γ-GT 23 U/l, alkaline phosphatase 119 U/l, GLDH 6.4 U/l). Ultrasonic examination showed no evidence of PVT, and serologic findings were still positive for HbsAg, but HBV-DNA were negative at two time-points. However, in October 1998, HBV-DNA was positive again, and liver enzyme levels were slightly higher (creatine 3.2 mg/dl, urea 87 mg/dl, total bilirubin 0.4 mg/dl, ASAT 15 U/l, ALAT 37 U/l, γ-GT 38 U/l, alkaline phosphatase 220 U/l, GLDH 6.2 U/l) without any evidence for recurrent PVT.

Discussion

Most centers report one year patient survival rates exceeding 80% after OLT. Thereafter, survival is not significantly altered, and OLT-related fatalities are rare. However, long-term complications such as nephrotoxicity, cardiovascular diseases, de-novo malignancies, and recurrent diseases gain in importance later on.

We reported on a patient with HBV reinfection 13 months after OLT. Nearly 2 years later, liver biopsy showed a slight portal fibrosis, and 10 months after that the patient presented with late PVT and moderate clinical symptoms.

Recurrent cirrhosis with decreased or retrograde portal flow is likely to cause late PVT after liver transplantation as well as in non-transplant populations. However, the reported patient presented no evidence for progression from portal fibrosis to cirrhosis, and normal portal flow measurements were reestablished after successful recanalization. Furthermore, technical complications, previous portal vein surgery, or splenectomy were assigned risk factors for early PVT following OLT [2, 9]. Although, the reported patient underwent splenic artery banding, postoperative portal flow never demonstrated values below normal range during a follow-up of more than three years. Therefore, a relation between both incidences is more than unlikely. In addition, neither postoperative ultrasound nor MRT angiography ever demonstrated any findings suspicious for portal vein stenosis. Finally, the importance of ongoing rejection for the development of PVT is somewhat controversial [7, 18, 24]. However, our patient showed no signs of either acute rejection at the time of PVT or chronic rejection thereafter, although he developed several rejection episodes in the course of time after OLT. In summary, the cause of late PVT in this patient remains unclear.

As causes for PVT after liver transplantation vary, clinical presentations differ greatly. In 1988, Burke et al. reported an unusual case of early PVT with only

mild clinical signs. In a two-week period of conservative management, a spontaneous lysis of the thrombus occurred [2]. However, in most cases, early PVT is followed by a serious deterioration of liver function and requires immediate retransplantation [9, 20]. In late PVT, liver function tests may not always be altered due to the development of de-novo hepatopetal collaterals [15, 25, 27]. In these cases, observation only is justified. Patients presenting with PVT and acute gastroesophageal bleeding have been suggested to be treated with surgical shunting or percutaneous transhepatic procedures [6, 10, 13, 16].

In non-transplant patients, several attempts of local or high-dose intravenous application of fibrinolytic agents have been successful [1, 3, 4, 11, 14, 21, 22]. Although, streptokinase (SK) and urokinase (UK) have been proven largely effective for thrombolytic therapies, both are characterized by limited thrombolytic potencies and major clinical disadvantages, compared to rt-PA [5]. While streptokinase has a high antigenicity, both SK and UK, but not rt-PA, lack a fibrin-specific action that causes systemic consumption of plasminogen and decreased thrombolytic efficacy, and may increase bleeding complications. However, in current thrombolytic high-dose regimens, rt-PA also demonstrates a partial loss of its fibrin-specificity. Encouraging reports of patients suffering from venous occlusive disease after bone marrow transplantation [26] led us to the non-invasive approach of systemic low dose rt-PA lysis. After a ten days course of 0.25 mg/kg per day rt-PA, a complete recanalization of the portal vein was achieved.

The use of anti-HBs-hyperimmunoglobulin significantly increased patient survival rates after OLT due to chronic HBV-infection [8, 17], but fatal outcomes following fulminant graft reinfection still often occurred. Hence, the introduction of effective anti-viral drugs additionally minimized the number of fatalities [23]. However, in our case progress to recurrent fibrosis was confirmed by biopsy. Therefore, we initiated ongoing studies using anti-viral drugs prior to OLT to decrease HBV-DNA, and combining anti-viral drugs and HBIG for reinfection prophylaxis.

In conclusion, we recommend the use of systemic low dose rt-PA in patients suffering from late PVT after OLT and presenting with moderate symptoms. Even the use of systemic low dose rt-PA in patients presenting with end-stage liver disease and PVT prior to OLT should be considered, carefully accounting for the individual risk of bleeding under such treatment.

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