

Hepatic Artery Thrombosis After Orthotopic Liver Transplant: A Review of the Same Institute 5 Years Later

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Abstract

Objectives: Summarize the experience of managing patients with hepatic artery thrombosis after orthotopic liver transplant in a single center.

Materials and Methods: A total of 726 adult patients who received a liver transplant at the Department of Organ Transplantation, the First Affiliated Hospital of Sun Yat-Sen University, between January 2004 and December 2009, were selected. Fourteen patients had hepatic artery thrombosis after the operation, and the clinical data of these patients were analyzed retrospectively.

Results: The incidence rate of hepatic artery thrombosis was 1.9% (14/726), and the mean time of onset was 10 days (range, 1-41 d) after surgery. Six patients had acute deterioration of liver function, 4 had bile leakage, 1 had hepatic abscess, and 3 had no symptoms. Three patients received urgent rearterialization, 2 received intra-arterial thrombolysis, 3 received combined urgent rearterialization and intra-arterial thrombolysis, and 6 patients received a retransplant. The mortality rate associated with hepatic artery thrombosis was 42.9% (6/14); 2 from biliary necrosis and secondary hepatic failure after urgent rearterialization; 1 from recurrent hepatic artery thrombosis and multiple organ failure after intra-arterial thrombolysis; 1 from renal failure and severe infection after combined urgent rearterialization and intra-arterial thrombolysis, and 2

from severe infection after retransplant. The other patients recovered and were followed for 18 to 66 months. Their liver grafts all functioned well with a patent artery. Two died from tumor recurrence at 18 and 29 months after transplant.

Conclusions: Hepatic artery thrombosis is a severe complication after liver transplant, which leads to graft loss and recipient death. Rearterialization as early as possible before irreversible biliary and liver parenchyma damage can avoid retransplant.

Key words: Transplantation, Complication, Retransplant, Rearterialization, Thrombolysis

Introduction

Hepatic artery thrombosis remains an important risk factor for graft loss or recipient death after orthotopic liver transplant—even in an era of mature transplant techniques and dedicated perioperative management. Retransplant is the only way to save the patients' life if the hepatic artery thrombosis is not discovered and treated in time.

We retrospectively studied the clinical data of a cohort of Chinese patients who had hepatic artery thrombosis after an orthotopic liver transplant at the same institute between 2004 and 2009 to summarize the experience of managing these patients with hepatic artery thrombosis.

Patients and Methods

General information

A total of 726 adult patients received orthotopic liver transplant at the Department of Organ Transplantation, the First Affiliated Hospital of Sun Yat-Sen University between 2004 and 2009, including 596 males and 130 females (mean age, 50.8 years; age range, 18-75 years). The immunosuppressive

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regimens after transplant included double regimen (steroid and tacrolimus) and triple regimen (steroid, tacrolimus, and mycophenolate mofetil). Interleukin-2 receptor monoclonal antibody induction was adopted in patients with high-risk factors before surgery, such as old patients (> 65-years-old), with hepatorenal syndrome, with a history of upper abdominal operation, and a model for end-stage liver disease score over 30. Furthermore, liver function and blood concentration of immunosuppressants were monitored after surgery.

Fourteen patients, including 13 males and 1 female, had hepatic artery thrombosis after the operation (mean age, 47.3 years; age range, 33-61 years). Of the 14 patients, 5 (35.7%) had a history of HBV-related liver cirrhosis, including 2 with a history of splenectomy and pericardial devascularization. Seven patients (7/14) had primary hepatocellular carcinoma, including 6 with a history of transcatheter arterial chemoembolization treatment. One case (1/14) had hilar cholangiocarcinoma, and another case (1/14) had acute liver failure. The mean model for end-stage liver disease score before transplant was 21.3 ± 10.2 . Before the study, the protocol was approved by our local institutional ethics committee; each organ donation and transplant in our center was performed strictly according to the guidelines of the 1975 Helsinki Declaration; and written, informed consent was obtained from all subjects.

Hepatic artery reconstruction

Microsurgical hepatic artery reconstruction was performed under a magnifier. The vascular intima was protected from inappropriate or excessive operative procedure. When trimming the liver graft, the main branches from the celiac artery to the proper hepatic artery were distinguished, especially in cases with arterial anatomic variants. After confirming normality, the splenic artery, the left gastric artery, the gastroduodenal artery, and the right gastric artery were ligated. Though the lower part of the bile duct is always nourished from the gastroduodenal artery, we routinely transect the common hepatic duct in hepatectomy, and we used the common hepatic duct (not the common bile duct) of the donor and the recipient for biliary reconstruction.

In this study, graft function recovery and biliary complications were acceptable compared with other reports. Anatomic variations of the hepatic artery

were found in 96 cases, including right hepatic arteries arising from the superior mesenteric artery (52/96), the right hepatic artery from the gastroduodenal artery (19/96), the accessory left hepatic artery from the left gastric artery (16/96), and a common trunk of the superior mesenteric artery and the celiac trunk arising from the abdominal aorta (9/96). All anomalous hepatic arteries and branches of celiac artery that matched the hepatic arteries in direction and size were anastomosed to form a single opening for spare use. Before that, it was important to confirm the diameter of the hepatic artery for reconstruction between the recipient and the donor, the blood volume and velocity, and the integrity of the vascular intima. In 19 recipients, proper hepatic artery and the common hepatic artery were found unsuitable for arterial reconstruction owing to impaired artery intima or poor blood volume or velocity. The upper renal arteries from the abdominal aortas of the 19 patients were separated after native hepatectomy. We used the iliac artery from the same donor as a bridge; the celiac trunk of the graft was anastomosed to the recipients' abdominal aorta via the bridge.

In patients diagnosed with hepatic artery thrombosis by Doppler ultrasound and hepatic arteriography after orthotopic liver transplant, the arterial anastomosis is ablated and the thrombus is removed as early as possible. The mural thrombus near the anastomosis was flushed with heparin. Reanastomosis of the hepatic artery is done after confirming patency of the hepatic artery.

Doppler ultrasound monitoring and anticoagulation

We performed daily, bedside ultrasonography for the first week, and in patients with a patent hepatic artery, daily examination was sufficient. If the hepatic artery velocity or volume was not satisfactory, a Doppler ultrasonography would be done by an expert to confirm these results. In patients with an unsatisfactory hepatic artery during the operation, we performed a Doppler ultrasonography twice a day. Anticoagulant therapy with low molecular heparin and prostaglandin E1 were given to keep activated partial thromboplastin time 10 seconds longer than the normal range when the peak blood flow velocity of the hepatic artery in the systolic stage was < 40 cm/second or the hepatic artery resistance index was less than 0.5 or higher than 0.8. Hematocrit

was kept below 30% during the early postoperative stage. Platelet transfusion was considered when the platelet count was less than $20 \times 10^9/L$. Additionally, anticoagulant therapy with warfarin and aspirin was adopted when the platelet count was beyond the upper limit of the normal range.

Results

Occurrence of hepatic artery thrombosis

Fourteen recipients had hepatic artery thrombosis after orthotopic liver transplant, which was diagnosed by hepatic arteriography. The incidence rate of hepatic artery thrombosis was 1.9% (14/726), and the mean time to onset of hepatic artery thrombosis was 10 days (range, 1 to 41 days) after surgery. In 13 cases (92.9%), hepatic artery thrombosis occurred within 30 days after orthotopic liver transplant. Among the 14 recipients, 6 had acute deterioration of liver function, 4 had bile leakage, 1 had hepatic abscess, and 3 had no symptoms (Table 1).

Treatment and prognosis of hepatic artery thrombosis

Three patients (3/14), accounting for 21.4%, received urgent rearterialization, and the patency of the artery is shown with Doppler ultrasound after surgery. Of the 3 patients, 1 was discharged with normal function of liver graft and patency of blood flow during follow-up. However, the patient died from recurrent tumors 29 months after the orthotopic liver transplant. Two patients had diffuse intrahepatic biliary necrosis, recurrent infection, and liver function deterioration after orthotopic liver

transplant and died from secondary hepatic failure 2 and 4 months after reoperation.

Two patients (14.3%) received intra-arterial thrombolysis. Of the 2 patients, 1 had rethrombosis complicated with septicemia 72 hours after intra-arterial thrombolysis and died from multiple organ failure 4 days later. The other was followed-up for 54 months, with the liver graft functioning well and the hepatic artery maintaining patency.

Three patients (21.4%) received combined urgent rearterialization and intra-arterial thrombolysis. The hepatic artery was opened after ablating the original anastomosis and removing the thrombus. Microsurgical, hepatic artery reconstruction was performed under 3.5-fold magnification. In cases with a vessel diameter > 3 mm, 8-0 Prolene suture was used with a continuous technique, and in cases with the vessel diameter < 3 mm, 9-0 Prolene suture was used with a separate technique. The mural thrombus near the anastomosis was flushed with heparin. Furthermore, transcatheter arterial injection with urokinase (500 000 U) was given immediately after rearterialization. The treatment time of urokinase in the 3 patients was 7, 5, and 5 days with the total dosage 2 100 000; 16 300 000; and 1 300 000 U. Of the 3 patients, 2 were discharged and followed for 30 and 27 months with normal hepatic function and a patent artery. In the remaining patient, hepatic blood flow was normal and the liver grafts gradually recovered to normal during follow-up. However, the patient died from severe infection and renal failure 12 days after rearterialization.

The remaining 6 patients (42.9%) received a retransplant. Of the 6 patients, 2 died from severe

Table 1. Information, treatment, and outcome of the 14 recipients with hepatic artery thrombosis.

Case	Sex	Age	Primary disease	Diameter of hepatic artery	Time of hepatic artery thrombosis	Manifestation	Mechanical factor	Treatment	Follow-up	Outcome
1	M	51	HCC	4 mm	12 d	BL	Intima injury	RT	18 m	Recurrence and died
2	M	43	HCC	2 mm	2 d	AHF	Intima injury	IAT	4 d	MODS and died
3	M	54	HBV	3 mm	7 d	AHF	Stenosis	RT	48 m	Survival
4	M	34	HBV	3 mm	41 d	BL	Splenic artery stealing	RT	41 m	Survival
5	M	56	AHF	3 mm	10 h	AHF	Stenosis	CRI	12 d	Died
6	F	61	HBV	2 mm	13 d	AHF	Stenosis	UR	2 m	Died of AHF
7	M	52	HCC	4 mm	8 d	—	Intima injury	CRI	27 m	Survival
8	M	39	HCC	5 mm	15 d	BL	Intima injury	RT	66 m	Survival
9	M	61	HCC	2 mm	16 d	AHF	Intima injury	UR	29 m	Recurrence and died
10	M	37	HBV	2 mm	5 d	—	Stenosis	CRI	30 m	Survival
11	M	52	HCC	3 mm	6 d	LA	Intima injury	RT	10 d	Died
12	M	33	CCA	2 mm	4 d	BL	Intima injury	RT	15 d	Died
13	M	35	HBV	5 mm	3 d	—	Splenic artery stealing	IAT	54 m	Survival
14	M	54	HCC	2 mm	7 d	AHF	Intima injury	UR	4 m	Died of AHF

Abbreviations: AHF, acute hepatic failure; BL, bile leakage; CCA, hilar cholangiocarcinoma; CRI, combined urgent rearterialization and intra-arterial thrombolysis; F, female; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IAT, intra-arterial thrombolysis; LA, liver abscess; M, male; RT, retransplant; UR, urgent rearterialization

infection 10 and 15 days after retransplant, and 1 died from recurrence of tumor 18 months after retransplant. Another 3 cases were followed for 66, 48, and 41 months with normal liver graft functioning and a patent artery.

In general, mortality associated with hepatic artery thrombosis in this group was 42.9% (6/14). Two died from biliary necrosis and hepatic failure after rearterialization, 1 from recurrence of hepatic artery thrombosis and multiple organ failure after intra-arterial thrombolysis, 1 from renal failure and severe infection after combined urgent rearterialization and intra-arterial thrombolysis, and 2 from severe infection after retransplant.

Discussion

Although surgical techniques and management during the perioperative period have improved during the last decade, the incidence rate of hepatic artery thrombosis remains high in adult recipients (3% to 5%),¹⁻³ while in children, the incidence may reach 10%.⁴⁻⁶ Blood supply to the liver parenchyma and biliary system in the early stage after orthotopic liver transplant mainly depends on the hepatic artery; and establishing effective collateral circulation needs at least 2 to 4 months.^{7, 8} Therefore, hepatic artery thrombosis may lead to ischemia and extrahepatic biliary necrosis.

There were many factors causing hepatic artery thrombosis, including anastomosis, arterial damage, anatomic variation, and diameter or unmatched vessels.^{9, 10} In this group of patients with hepatic artery thrombosis, 6 patients with hepatocellular carcinoma had transcatheter arterial chemoembolization before transplant. The arterial intima might be damaged by repeated puncture. Patients with liver cancer are always in a hypercoagulable state during the perioperative period. Unlike patients with liver cirrhosis or liver failure, this group of patients would have a higher risk of dealing with hepatic artery thrombosis after transplant. Because the sample was small in this study, it is unreasonable to establish transcatheter arterial chemoembolization as a risk factor. Further prospective multicenter studies to investigate the risk factors for hepatic artery thrombosis are needed.

According to the onset time, early hepatic artery thrombosis occurred within the first 30 days after orthotopic liver transplant, while late hepatic artery thrombosis occurred beyond 30 days after orthotopic

liver transplant.¹¹⁻¹² Clinical presentation of hepatic artery thrombosis included fever, fatigue, and an increase in transaminase and bilirubin. Septicemia and acute liver graft failure were observed in severe conditions, whereas in early hepatic artery thrombosis, some patients were clinically asymptomatic. Of the 14 patients, 3 were clinically asymptomatic. Therefore, dynamic monitoring of liver graft blood flow with color Doppler ultrasound in the early stage after orthotopic liver transplant was of great importance for detecting hepatic artery thrombosis as early as possible.^{13, 14}

The blood supply to the liver parenchyma and biliary system in the early stage after orthotopic liver transplant depends mainly on the hepatic artery. The longer the ischemic time, the lower the survival rate of the liver graft. Recovery of blood flow as soon as possible is important for rescuing the graft as well as the patient's life.¹⁵ Urgent thrombectomy and hepatic artery reconstruction for early diagnosis of hepatic artery thrombosis are recommended as first choice by the transplant center of University of Pittsburgh Medical Center.¹⁶ Based on previous experience, retransplant is avoidable with urgent rearterialization in early diagnosed patients before irreversible biliary and liver parenchyma damage.^{17, 18}

Three of the 14 patients with hepatic artery thrombosis in our study received rearterialization. Of 3 patients, 2 who presented with acute liver function deterioration had irreversible biliary damage after rearterialization. There have been many successful case reports about systemic thrombolysis therapy for hepatic artery thrombosis.^{1, 25} However, anastomotic hemorrhage, and even systemic bleeding, may occur after systemic thrombolysis. Rethrombosis also remains high. Therefore, systemic thrombolysis is a controversial choice for the patients.¹⁹⁻²¹

As opposed to systemic thrombolysis, intra-arterial thrombolysis was effective with less risk of bleeding. Likewise, early diagnosis is also essential for the effectiveness of intra-arterial thrombolysis.²² Two of the 14 patients received intra-arterial thrombolysis, 1 had acute deterioration of liver function with hepatic artery thrombosis, and the other one was clinically asymptomatic. Patency of intrahepatic arterioles and collaterals were observed after intra-arterial thrombolysis, but 1 patient still died from rethrombosis after the treatment. Three of the 14 patients received combined therapy. One was diagnosed with hepatic artery thrombosis by color Doppler ultrasound 10

hours after the orthotopic liver transplant. Another 2 patients with sharp increase in liver enzymes 5 and 8 days after the orthotopic liver transplant were found to have absent hepatic arterial blood flow by color Doppler ultrasound study. The onset and diagnosis of hepatic artery thrombosis in the above 3 patients were within 24 hours after orthotopic liver transplant, without diffuse hepatic microthrombosis. Urgent rearterialization and intra-hepatic thrombolysis were performed through hepatic artery catheterization. All 3 patients had no recurrence of hepatic artery thrombosis, with their liver grafts functioning well—although 1 died from renal failure owing to severe infection.

Six of the 14 patients received retransplant. Of the 6 patients, 4 had hepatic artery thrombosis with bile leakage, and 1 had hepatic abscess. Irreversible biliary damage occurred in these 5 patients. Another had acute deterioration of liver function with poor coagulation. Therefore, retransplant was the only choice for these 6 patients. Early hepatic artery thrombosis has been an indication for urgent retransplant, but the survival rate is only 30% to 50%.²³ In our study, 2 patients (33.3%) died during the perioperative period. Meanwhile, the problems inherent in a shortage of donor organs and the high cost for retransplant are unsolved.

Owing to the low incidence of hepatic artery thrombosis after orthotopic liver transplant, 14 cases were collected in our research. It was difficult to compare the advantages and disadvantages among different therapies with only a few cases in a single center. A multicenter observation with a large population might be helpful for us to determine the statistical difference between treatments.

Although hepatic artery thrombosis is rare, treatment of hepatic artery thrombosis after orthotopic liver transplant is not ideal. Prophylaxis of hepatic artery thrombosis with close monitoring is of great importance.^{24, 25} In our experience, recovery of blood flow of hepatic artery thrombosis within 24 hours, during which diffuse microthrombus is not formed in the liver graft, can prevent retransplant. Additionally, combined rearterialization and intra-arterial thrombolysis was more effective than single therapy.

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