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Original Article

Value of percutaneous transhepatic cholangioscopy in the treatment of biliary cast after liver transplantation

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Abstract: Objective: This study aims to investigate the value of percutaneous transhepatic cholangioscopy (PTCS) in the diagnosis and treatment of biliary casts after liver transplantation. Methods: The clinical data of 17 patients who had biliary casts after liver transplantation between April 2008 and January 2013 were analyzed. Result: Of the 17 patients with biliary casts after liver transplantation, 2 patients had biliary casts in the common bile duct, which were treated by endoscopic retrograde cholangiopancreatography (ERCP). Among the remaining 15 patients, 5, 6, and 4 patients had right intrahepatic bile duct, left intrahepatic bile duct, and intrahepatic and extrahepatic widespread biliary casts, respectively. PTCS was conducted 96 times in total, and the biliary casts were successfully cleared in 13 out of 15 patients using the PTCS technique, showing satisfactory treatment outcomes (effective rate, 86.67%). One patient required a long-term drainage tube due to persistent fever when his drainage tube was clipped, even though the biliary casts were cleared. Moreover, one patient underwent a second liver transplantation due to vanishing bile duct syndrome. During the postoperative follow-up of 10-30 months, one patient presented recurring biliary casts in the common bile duct and underwent ERCP in the 15th postoperative month. One patient died due to biloma in 6 months postoperatively. The rest of the patients are in good condition. Conclusion: The PTCS technique is a safe and effective method to treat biliary casts after liver transplantation, and should be the preferred method used clinically.

Keywords: Liver transplantation, biliary cast, electronic choledochoscope, percutaneous transhepatic cholangioscopy

Introduction

Biliary casts were first described in 1975 by Waldram, an American physician [1]. In 1977, Starzl formally put forward biliary cast syndrome (BCS) [2]. BCS is characterized by the biliary tree, including the intrahepatic and extrahepatic bile ducts, being filled with cast necrotic material known as biliary casts after orthotopic liver transplantation, which causes obstruction and consequent serious complications, with clinical implications such as multiple intrahepatic biliary strictures, ductal dilatation, intrahepatic abscesses, and biliary anastomotic leakage. The incidence of BCS was originally reported to be approximately 7% to 30% [2]. In recent years, the incidence rate has significantly decreased due to improvements in graft harvesting and preservation; however, BCS still develops in 4% to 18% of all liver transplant recipients [3, 4].

The clinical symptoms of BCS usually include high fever, jaundice and cholestatic liver enzyme elevation, which are similar to the symptoms observed in some patients with intrahepatic bile duct stones. However, BCS after liver transplantation differs from traditional biliary calculi in the etiology, pathogenesis, and physical and chemical properties. Proposed etiological factors of BCS include biliary injury, cellular rejection, ischemia reperfusion injury, biliary drain, parenteral nutrition, and biliary infection [3, 5-7].

BCS often cause serious consequences such as irreversible liver damage, liver graft loss, and liver retransplantation; and the retransplantation rate and mortality are high. The pathogenesis of cast formation is not clearly understood, and hence, clinical prevention and treatment of BCS are difficult.

Table 1. General information of patients

Case	Gender	Age (yr)	Primary disease	Type of liver transplantation surgery	Time of BCS (weeks)	Distribution of BC	Times of PTCS
1	M	46	Hepatitis b-associated cirrhosis	Standard	12	C	6
2	F	54	Primary biliary cirrhosis	Piggyback	16	D	8
3	F	53	Primary biliary cirrhosis	Standard	15	D	9
4	F	33	Primary carcinoma of the liver	Standard	20	A	-
5	M	54	Primary carcinoma of the liver	Piggyback	15	C	5
6	M	58	Primary carcinoma of the liver	Standard	14	A	-
7	M	57	Hepatitis b-associated cirrhosis	Standard	16	B	7
8	F	47	Hepatitis b-associated cirrhosis	Standard	20	D	8
9	M	48	Hepatitis b-associated cirrhosis	Standard	17	B	4
10	M	55	Hepatitis b-associated cirrhosis	Standard	18	B	6
11	F	51	Hepatitis b-associated cirrhosis	Standard	32	C	6
12	M	62	Alcoholic cirrhosis	Standard	16	B	7
13	M	56	Hepatitis b-associated cirrhosis	Standard	17	C	5
14	M	52	Primary carcinoma of the liver	Standard	24	B	7
15	F	4	Congenital biliary atresia	Standard	15	D	8
16	M	42	Hepatitis b-associated cirrhosis	Standard	16	C	4
17	M	50	Primary carcinoma of the liver	Standard	17	C	6

M: male; F: female; BCS: biliary cast syndrome; BC: biliary cast; A: Common bile duct; B: The right hepatic duct; C: The left hepatic duct; D: Bile duct of liver inside and outside.

Timely diagnosis and treatment of biliary casts after liver transplantation is particularly important for the maintenance of graft function. Biliary casts after liver transplantation most commonly occur 3 to 4 months after the transplantation, or even later in some cases. During this period, the T tube is often withdrawn, thereby no longer enabling choledochoscopy. Due to BCS patients frequently experiencing long-term fever and liver dysfunction, their basic state is generally poor. Thus, placing a T tube by reoperation biliary probe may induce serious trauma in these patients, which poses a substantial risk to their health.

Intrahepatic bile duct casts are difficult to treat by endoscopic retrograde cholangiopancreatography (ERCP). Furthermore, patients treated by ERCP commonly present with recurring chills and fever, owing to reflux cholangitis induced by Oddi sphincter dysfunction after ERCP. Percutaneous transhepatic cholangioscopy (PTCS) is a reasonable choice for the treatment of hepatolithiasis in lieu of ERCP or traditional surgery. PTCS is not only an effective treatment of casts in both the intra- and extrahepatic bile ducts, but also less painful than ERCP. Thus, it can be speculated that PTCS is in fact the most appropriate treatment for BCS. In this study, we retrospectively analyzed patients with biliary casts after liver transplantation treated by PTCS in order to objectively evaluate the effectiveness of this approach.

Methods

Patients

From April 2008 to January 2013, there were 17 cases of BCS after orthotopic liver transplantation in our hospital. These patients comprised 11 males and 6 females, with an age range from 4 to 62 years. The primary diseases were hepatitis B-associated cirrhosis (8 cases), primary biliary cirrhosis (5 cases), primary carcinoma of the liver (2 cases), alcoholic cirrhosis (1 case), and congenital biliary atresia (1 case). Of these 17 patients, 2 patients underwent a piggyback orthotopic liver transplantation and 15 underwent standard orthotopic liver transplantation. This study was conducted in accordance with the declaration of Helsinki and the approval from the Ethics Committee of Dalian University. Written informed consent was obtained from each participant.

The patients presented with systemic jaundice, repeated high fever, and chills in 12 to 32

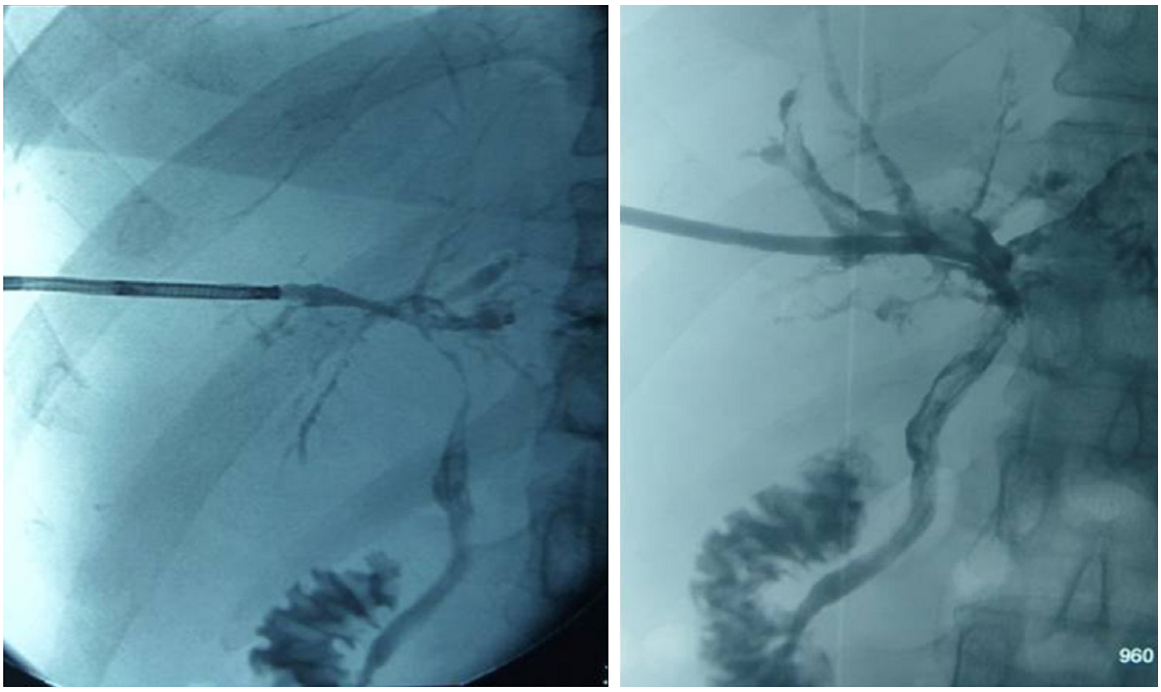

Figure 1. Cholangiography of biliary cast syndrome.

weeks postoperatively. Accordingly, they were suspected to have BCS. Subsequently, the biochemical index and sonographic appearance were assessed, and computed tomography, and/or magnetic resonance imaging were performed to make an initial diagnostic evaluation and to exclude other etiologies of liver failure (hepatic artery stenosis, vascular thrombosis, and liver hypoperfusion) [8]. Finally, the diagnosis of cholestasis was corroborated by cholangiography. The clinical data are shown in **Table 1**.

Percutaneous transhepatic cholangial drainage (PTCD)

The position of the puncture point was decided according to the preoperative auxiliary examination. If the casts were in the right lobe of the liver, the puncture was generally made at the intersection of the left axillary midline and seventh or eighth intercostal, while the costophrenic angle was avoided. At the same time, a metal instrument such as a needle detector was placed on the xiphoid process as an indicator. If the casts were concentrated in the left lobe of the liver, the puncture point was made under the right subxiphoid region. The puncture was performed under X-ray fluoroscopy or color Doppler ultrasound surveillance. In both the conventional intercostal (right biliary branches) and subxiphoidal (left biliary branches) approaches, after PTCD of the biliary tree was established, the biliary casts were visualized by cholangiography. Subsequently, an 8.5-Fr drainage catheter (Cook Incorporated, USA) was placed for draining of the biliary system in order to decrease the cholestasis and for treating the inflammation (**Figures 1**, **2**).

Fistula expansion

In a second procedure (1 month after the first PTCD implantation), the sinus was dilated and the biliary drain was exchanged for a wider drain once every 2 weeks under X-ray fluoroscopy guidance. First, a high performance guidewire (0.9 mm × 180 cm, Boston Scientific Corporation, USA) was placed in the biliary drain, after which the 8.5-Fr drainage catheter was removed. Next, the sinus was gradually dilated using a guidewire until it reached the same width as a 12-Fr drainage catheter (Cook Incorporated, USA). Lastly, a 12-Fr drainage catheter was placed for draining. After 2 weeks, a 16-Fr drainage catheter (Cook Incorporated, USA) was placed, using the same method of expansion. The drainage tube was fixed on the skin to prevent it from moving. If the bile drain-

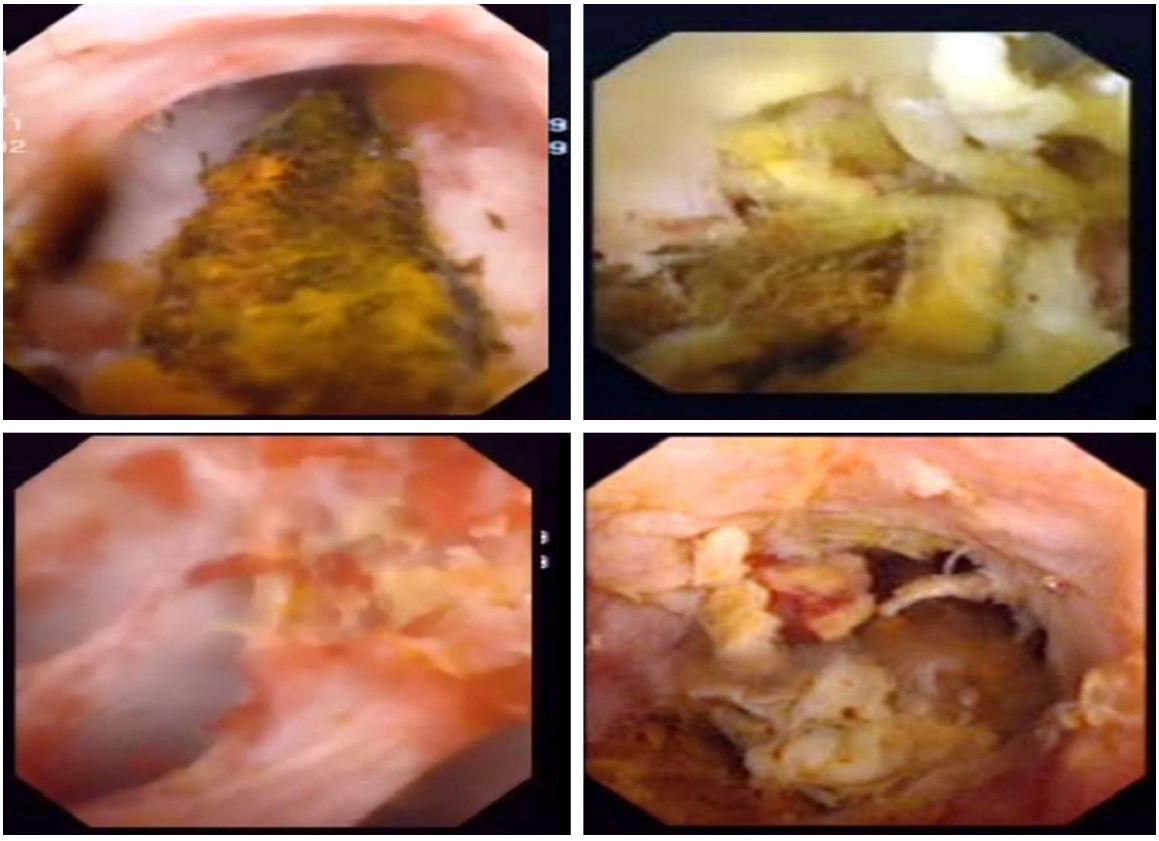

Figure 2. Through choledochiscope, it was shown that the bile ducts were filled with casts and the bile duct mucosa was necrosis.

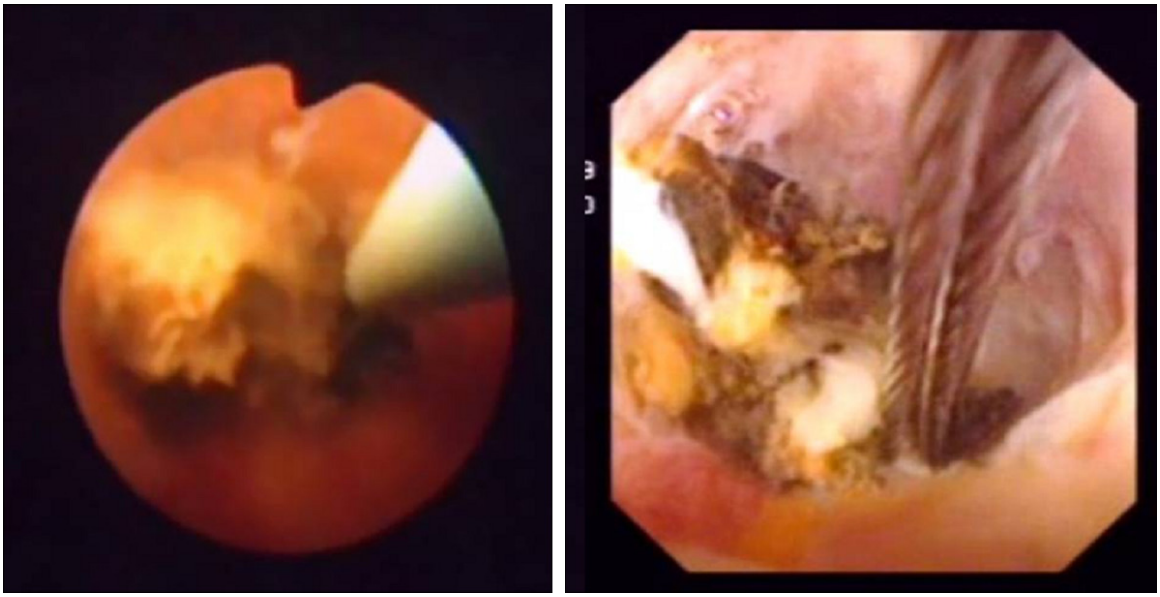

Figure 3. Biliary casts were taken out with a basket.

age was obstructed or the patients experienced recurrent high fever or jaundice, the position of the tube was timely adjusted according to the imaging findings of the drainage tube.

Figure 4. Various forms of the biliary cast.

PTCS

The third procedure was the PTCS itself. A choledochoscope was placed into the bile ducts through the sinus. The hepatic portal was checked, after which, in turn, the hepatic duct, common bile duct, and intrahepatic bile ducts were all checked. If a cast was found, it was removed using an extraction basket (Cook Incorporated, USA) or biopsy forceps (Olympus Medical Systems Corporation, Japan) (**Figure 3**).

Statistical analysis

The analyzed liver function indices of all patients, including alanine aminotransferase (ALT), γ-glutamyltransferase (GGT), alkaline phosphatase (ALP), total bilirubin (TBIL), and direct bilirubin (DBIL), obtained before and after treatment, were presented as median values (range). The data were analyzed by the Mann-Whitney U test using SPSS 17.0 software (SPSS Inc., USA), with $P<0.05$ considered statistically significant.

Results

Imaging of PTCS

As shown in our previous report [9], intrahepatic biliary tract filling defects were found in the patients with BCS (**Figures 1**, **2**). Among the 17 patients analyzed in the present study, 2 patients had biliary casts in the common bile duct, which were treated by ERCP. Among the remaining 15 patients, 5, 6, and 4 cases showed right intrahepatic bile duct, left intrahepatic bile duct, and widespread intrahepatic and extrahepatic biliary casts, respectively (**Figure 1**). In addition, 8 cases showed concomitant bile duct stricture (**Table 1**).

Treatment of PTCS

In all patients, choledochoscopy revealed that the bile ducts were filled with casts and that the bile duct mucosa was necrosed (**Figure 2**). The biliary casts were removed using an extraction basket or biopsy forceps (**Figure 3**). The forms of the biliary casts included “antler” shape, “leafless tree” shape, block shape, and sheets (**Figure 4**). For the 15 patients, a total of 96 times of PTCS was conducted. We successfully cleared the biliary casts in 14 of the 15 patients using the PTCS technique. Thirteen patients showed satisfactory outcomes, with the fever and jaundice disappearing, improving liver function, and recovering biliary tree to normal, as assessed by cholangiography (**Figure 5**). Furthermore, in these patients, choledochoscopy revealed that the bile duct mucosa was

Figure 5. "Biliary tree" recovered normal by cholangiography after treatment.

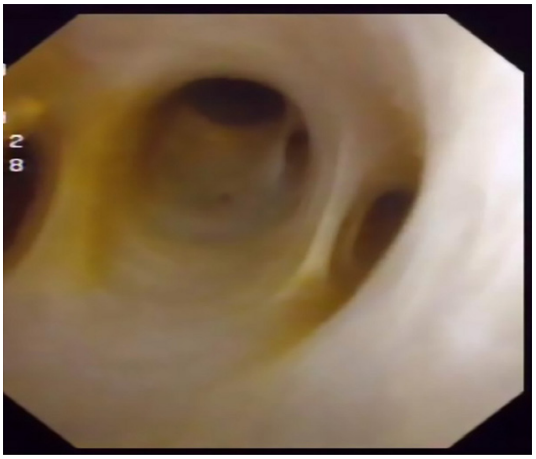

Figure 6. Under choledochoscope, bile duct mucosa is smooth, reddish, lumen is circular or elliptic, fresh bile is secreted out, after treatment.

smooth and reddish, the lumen was circular or elliptic, and the fresh bile was secreted (**Figure 6**). Subsequently, the drainage catheter was removed. Overall, the effective rate of PTCS was 86.67%. Although the biliary cast was cleared, as confirmed by cholangiography and choledochoscopy, one patient required a thinner drainage catheter for an extended time due to a persistent fever after the drainage catheter was clipped; the body temperature recovered to normal after the drainage catheter was reopened. One patient with disappearing intrahepatic bile duct syndrome had to undergo a secondary liver transplantation. There were no cases of biliary fistula, bleeding, infection, or other complications.

Liver function was improved by PTCS treatment

Compared with those before the treatment, the TBIL, DBIL, and ALT levels were significantly decreased after the treatment ($P<0.05$); however, there were no significant differences between before and after treatment in terms of ALP or GGT ($P>0.05$; **Table 2**).

Follow-up

The patients were followed up for 10 to 30 months after the operation. During the follow-up period, biliary casts in the common bile duct were found in one patient, and were removed by ERCP in the 15th postoperative month. One patient developed biloma in the 6th month after treatment and died while waiting for a secondary liver transplantation. All other patients were in good condition at the latest follow-up.

Discussion

Traditionally, surgical management and retransplantation are the mainstay of treatment in the early phase of BCS. Patients with BCS typically experience chronic fever, poor liver function and general weakness. BCS almost always occurs within the first year of liver transplantation, and more than 70% of casts are identified in the first 16 weeks post-transplantation [3, 10]. The patients in this study showed biliary casts between 12 to 32 weeks post-transplantation, and 70% of the patients had bile casts already at 14 to 18 weeks, which is similar to that reported in previous studies [3, 10]. The success rate of liver transplantation treating BSC has been reported to be greater than 85% in some studies; however, this procedure is nonetheless associated with high mortality and substantial morbidity [1, 11]. Furthermore, donor livers are rare, which is limiting retransplantation. With the development of endoscopic techniques, ERCP has been successfully used for removal of biliary casts. In addition, a variety of techniques, including biliary sphincterotomy, balloon/basket extraction, electrohydraulic, and mechanical lithotripsy, have also been used through ERCP to extract biliary casts [5, 12, 13]. However, the success rates of the different endoscopic techniques vary from 25% to 60% [5, 12, 13]. Especially, this kind of technique is generally highly effective in the treatment of calculi in the extrahepatic bile duct, but

Table 2. The change of liver function index

	TBIL (umol/L)	DBIL (umol/L)	ALT (U/L)	ALP (U/L)	GGT (U/L)
Before treatment	87.15 (13.8~212.9)	29.55 (0~102.9)	88 (53~229)	356.5 (63~1500)	379.5 (107~1380)
After treatment	25.95 (15.9~315.4)	0 (0~176.5)	54.5 (26~102)	317 (92~1329)	250.5 (28~1400)
P	0.014	0.007	0.011	0.922	0.491

TBIL: total bilirubin; DBIL: direct bilirubin; ALT: alanine aminotransferase; ALP: alkaline phosphatase; GGT: γ-glutamyltransferase.

cannot extract biliary casts from the intrahepatic bile duct.

PTCS is a series examination and treatment that can be used in both the intrahepatic and extrahepatic bile ducts. During PTCS, a drainage catheter is first placed in the bile duct percutaneously (PTCD). Next, the sinus is dilated step by step to accommodate the choledochoscope into the bile duct for examination and treatment. Thus, although ERCP cast retrieval is typically the first choice strategy, ERCP treatment is difficult to achieve due to the complexity of the biliary tract and casts after orthotopic liver transplantation. In this situation, PTCS can be used to treat BCS in failed or unsuitable cases of ERCP [14, 15]. For example, Srinivasaiah [6] reported on a case of successful biliary cast treatment using PTCS in a patient with hepaticojejunostomy, which is unsuitable to treat with ERCP. Compared with ERCP, PTCS can not only attempt complete removal of the casts in the intrahepatic bile ducts, but also directly visualize the intrahepatic and extrahepatic ducts, thus allowing easy identification of the biliary anastomotic healing degree, and the presence of narrowing and bile duct mucosa.

In this study, in patients with BCS, it was shown that there were sheet and strip filling defects along with "leafless tree"-shaped casts and segmental strictures in the intrahepatic bile duct by cholangiography and PTCS. In some cases, the intrahepatic bile duct was thin and distended, and parts of the intrahepatic bile ducts had even disappeared at this stage. Cholangiography is a commonly used diagnostic method following biliary surgery; however, for casts in liver transplant recipients, the diagnostic results of cholangiography are often unclear and unreliable, which can lead to missed diagnoses and misdiagnoses, and consequently result in incorrect treatment. Cases that are negative upon cholangiography can be successfully diagnosed by fibrocholedochoscopy. In the present study, choledochoscopy was capable of revealing bile ducts filled with floccules or gallstones, which were brown in color with linear, columnar, or tree-like shapes, and with surfaces as rough as withered bark or in a honeycomb structure. The gallstones felt like sponge, and the cut surface showed hollowness and layers. Hence, our results suggest that the combination of cholangiography and fibrocholedochoscopy is more accurate, reliable, and less prone to misdiagnosis.

In the process of removing casts by choledochoscopy, the intrahepatic bile ducts presented serious damage, including congestion, erosion, ulcers, and partial or complete exfoliation of the bile duct mucosa. Because there were more cases of serious biliary non-anastomotic stenosis than anastomotic stenosis, the authors speculate that stimulation of biliary casts after liver transplantation resulting in damage to the bile duct mucosa may represent the root cause of the recurrent high fever and abnormal liver function observed in these patients. Therefore, besides removing all casts should be considered the primary treatment, promoting the regrowth of the bile duct mucosa is also required.

Damage of the bile duct mucosa can lead to bleeding. In our institution, every operation was controlled in 1 hour in order to prevent damage to the bile duct mucosa and to reduce the potential complications such as bleeding. At the same time, to avoid fractures of the fistula, repeated PTCS procedures were performed 2 weeks apart. This study showed that the biliary casts after liver transplantation tended to be multiple and difficult to be removed. Accordingly, the period of treatment was long, with each case requiring an average of at least 6 PTCS operations. After the casts had been completely removed, the mucosa of the intrahepatic bile duct showed different degrees of improvement. In most cases, the bile duct mucosa gradually became smooth, fresh bile was eventually secreted, and the biliary tree returned to nor-

mal, as determined by cholangiography. In addition, during the interval operation, continuous daily application of metronidazole, along with gentamicin administration and salt flushing of the biliary duct were performed through the PTCD tube, which could effectively control bile duct inflammation and had the advantages of removing the casts and repairing the bile duct epithelium.

In this study, the hepatic function indices of patients with biliary casts, such as TBIL, DBIL, ALT, ALP, and GGT, were aberrantly increased before the operation. But during the treatment, the levels of TBIL, DBIL, and ALT were found to be gradually reduced. Though they were not completely returned to normal, significant improvements compared with the preoperative levels were observed. Moreover, the clinical symptoms of fever and jaundice also disappeared. However, complete removal of the casts and improved liver function do not mean that the tube can be pulled out. In this study, one patient required a drainage tube for a long time, owing to a persistent fever when his drainage tube was clipped, despite the biliary casts being cleared. Hence, we believe that the PTCD should first be intermittently clipped, and that the patient's symptoms and liver function index should be carefully observed. If the patient presents with a fever or hyperbilirubinemia, the drainage tube must be reopened, and treatments aimed at protecting the liver and reducing inflammation must be performed. We believe that the drainage tube should not be pulled out until the following conditions have been met: (1) the patient has no fever or jaundice after the drainage tube has been clipped for a week; (2) the biliary tree is developing normal, as determined by biliary imaging by cholangiography; and (3) upon choledochoscopy, the bile duct mucosa is smooth and reddish, the lumen is circular or elliptic, and fresh bile is secreted. Furthermore, the tube must be gradually withdrawn by only 1-2 cm daily until it is completely uprooted.

Complete clearance of the biliary casts is important, as this is related to a better long-term outcome. The incidences of recurrent cholangitis or retransplantation are significantly higher in patients with incompletely removed biliary casts compared to those without remaining biliary casts. The success rate of PTCS for the treatment for hepatolithiasis has been reported as 80% to 85.3%, and the complication rate is only 4% [16-18]. In this study, the success rate of PTCS for the treatment BCS was 86.67%, which is in accordance with the previous reports. At the same time, there were no complications during the treatment. During the follow-up of 10 to 30 months, one of the 13 patients successfully treated by PTCS experienced recurrent biliary casts, which were treated by ERCP; the recurrence rate was 6.67%. In cases of failure of the endoscopic or percutaneous approach, surgical intervention is necessary, and retransplantation remains the last treatment option for this condition [19]. In the present study, there was one patient who required a secondary liver transplantation due to failure of PTCS.

In conclusion, our results indicate that PTCS represents a safe and effective means for diagnosis and treatment of patients with BCS after orthotopic liver transplantation, particularly in cases with intrahepatic duct casts. This technique deserves more attentions and, due to its high success rate, should be widely applied clinically.

Disclosure of conflict of interest

None.

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