Original Article

Biliary Cast Syndrome: Hepatic Artery Resistance Index, Pathological Changes, Morphology and Endoscopic Therapy

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Abstract

Background: Biliary cast syndrome (BCS) was a postoperative complication of orthotopic liver transplantation (OLT), and the reason for BSC was considered to relate with ischemic type biliary lesions. This study aimed to evaluate the relationship between BCS following OLT and the hepatic artery resistance index (HARI), and to observe pathological changes and morphology of biliary casts.

Methods: Totally, 18 patients were diagnosed with BCS by cholangiography following OLT using choledochoscope or endoscopic retrograde cholangiopancreatography. In addition, 36 patients who did not present with BCS in the corresponding period had detectable postoperative HARI on weeks 1, 2, 3 shown by color Doppler flow imaging. The compositions of biliary casts were analyzed by pathological examination and scanning electron microscopy.

Results: HARI values of the BCS group were significantly decreased as compared with the non-BCS group on postoperative weeks 2 and 3 ($P < 0.05$). Odds ratio (*OR*) analysis of HARI 1, HARI 2, HARI 3 following the operation was >1 (*OR* = 1.300; 1.223; and 1.889, respectively). The *OR* of HARI 3 was statistically significant (*OR* = 1.889; 95% confidence interval = 1.166–7.490; $P = 0.024$). The compositions of biliary casts were different when bile duct stones were present. Furthermore, vascular epithelial cells were found by pathological examination in biliary casts.

Conclusions: HARI may possibly serve as an independent risk factor and early predictive factor of BCS. Components and formation of biliary casts and bile duct stones are different.

Key words: Biliary Cast Syndrome; Endoscopic Therapy; Hepatic Artery Resistance Index; Ischemic Type Biliary Lesions; Orthotopic Liver Transplantation

Introduction

Biliary complications from liver transplantation present in 5.8–30.0% of cases, and the incidence is related to the characteristics and type of donor, cold ischemia time, and the type of bile duct anastomosis, among other factors.[1-5] Biliary cast syndrome (BCS) after orthotopic liver transplantation (OLT) is often caused by biliary obstruction and cholangitis, and the incidence of which currently ranges from 3% to 18% and between 5% and 25% of OLT recipients,[6,7] which is less frequent than the incidence of biliary sludge and occurrence of bile duct stones. Characteristic pathological changes include damage to the biliary epithelium, collagen fibrous tissue hyperplasia, and formation of biliary casts. Waldram *et al.* reported BCS in 1975s,[8] and it represents a serious complication following OLT. Furthermore, there is a close association between patient death from liver transplantation, graft damage or loss, and additional liver transplants.

Multiple intrahepatic and extrahepatic biliary strictures and dilatation, intrahepatic abscesses, and biliary anastomotic leakage were characteristic of the presentation of BCS. The clinical symptoms of BCS usually include high fever, jaundice, and cholestatic liver enzyme elevation, which resemble the symptoms that are observed in some patients with intrahepatic bile duct stones. An endoscopic strategy is the first choice for managing biliary complications, 83% of patients with biliary stricture were treated by endoscope with a success rate of 57%; additionally, 38% of patients with biliary leakage were indicated for endoscopic biliary drainage.[9]

In the current report, we studied the relationship between BCS and the hepatic artery resistance index (HARI). Meanwhile, studies of the correlation between BCS and ischemic type biliary lesions (ITBL) following OLT were investigated. The pathological changes of biliary casts after OLT by optical

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microscopy and morphological observation of biliary casts by scanning electron microscopy were also determined.

Methods

Diagnosis and treatment of biliary casts

We evaluated 18 confirmed cases with a history of BCS after OLT, and who had undergone cholangiography with T-tube fistula or endoscopic retrograde cholangiopancreatography (ERCP). This study considered 14 males and 4 females, with a mean age of 50.9 years (range: 45–68 years), who had all undergone deceased donor liver transplantation from 2008 to 2014. This group of patients presented with BCS, had also undergone OLT at least 3 months later, and not beyond 12 months after diagnosis of BCS.

Of the 18 patients, 12 cases of cirrhosis, 4 cases of hepatitis B-induced cirrhosis, and 2 cases of primary liver cancer were identified during the decompensated period. Patients with T-tube fistula were diagnosed by the insertion of a choledochoscope directly into the common bile duct, and patients without evidence of a T-tube fistula were evaluated preferentially by ERCP. In addition, biliary casts were taken out using a basket and a balloon catheter in 6 cases by choledochoscope, and 12 cases by duodenoscope.

Hepatic artery resistance index

HARI is measured by ultrasonography Doppler, including 18 cases of BCS after OLT, and 36 cases of non-BCS. In the corresponding period, postoperative HARI was detected on weeks 1, 2, and 3 by color Doppler flow imaging (CDFI) using the Aloka Prosound F75 (Hitachi Ltd., Japan).

Statistical analysis

Differences of HARI mean values between BCS group and non-BCS group on postoperative different stages were analyzed by the nonparametric Mann–Whitney statistical analysis, and odds ratio (*OR*) of HARI on postoperative different stages was analyzed by logistic regression analysis. $P < 0.05$ was considered as statistically significant. All computations were performed with SPSS Complex Samples™ 17. 0 software (SPSS Inc., USA).

Pathological changes of biliary casts

Histological sections of biliary casts were H and E stained with standard procedures and compared to intrahepatic bile duct mixed type stones obtained from non-OLT-patients.

Morphological observation of biliary casts

Morphological observations of the biliary casts and intrahepatic bile duct mixed type stones from non-OLT-patients were examined using a Model S-4800 field emission scanning electron microscope (Hitachi Ltd., Japan) by standard procedures at 2 kV.

Results

Cholangiography with T-tube fistula or ERCP showed intrahepatic and extrahepatic biliary strictures or alternate dilatation, columnar and dendritic shapes of biliary casts within the intrahepatic and extrahepatic bile duct system [Figure 1].

Results of the nonparametric Mann–Whitney statistical analysis of HARI, and HARI on postoperative weeks 2 and 3, showed there were statistically significant differences between the non-BCS and BCS patients ($P < 0.05$; Table 1 and Figure 2). Postoperative HARI was declining, and there was a higher incidence of biliary complications.

Results of logistic regression analysis of HARI, and *OR* of HARI 1, HARI 2, HARI 3 at the postoperative stage were >1 (*OR* = 1.300; 1.223; 1.889, respectively), which suggested that HARI might be an independent risk factor. The *OR* of HARI 3 showed a statistically significant difference (*OR* = 1.889; 95% confidence interval = 1.166–7.490; $P = 0.024$; Table 2; Figure 2). According to the statistical analyses, we confirmed that when HARI = 0.64, this represents a critical value, at which point biliary cast complications occurred, and the value was within the normal range too (0.55–0.80; Figure 2). When HARI >0.64, it is marked as 1, as compared with HARI ≤0.64 when it is marked as 0. This meant that when HARI scores were smaller, the comparative risks were greater. The risk degree of HARI ≤0.64 was 1.889 times than HARI >0.64.

The compositions of biliary casts were comparatively different in the context of bile duct stones. The vascular epithelial cells were identified by pathological examination in biliary casts [Figure 3]. Morphology of biliary casts and bile duct stones was determined by scanning electron microscopy. Biliary casts in the shape of filamentous structures were observed, and the structures were relatively loose. Bile duct stones in the shape of a spherical structure with additional dense structures were also seen [Figure 4].

Discussion

Liver transplantation is one of the most important surgical interventions in the treatment of end-stage liver disease. Diagnosis, treatment, and prevention of bile

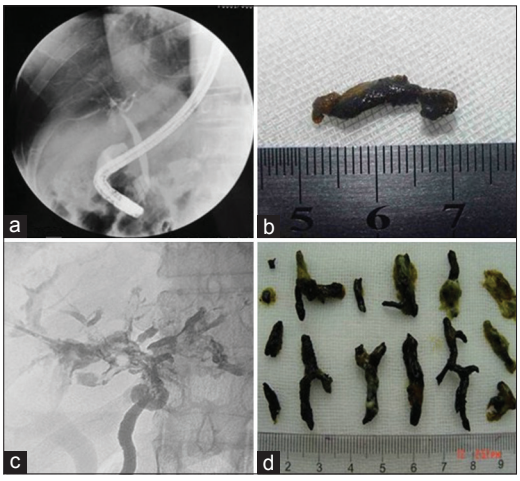

Figure 1: Diagnosis and treatment of biliary casts. (a) Endoscopic retrograde cholangiopancreatography; (b) Small biliary casts within the intrahepatic biliary duct system; (c) Intrahepatic and extrahepatic biliary strictures or alternate dilatation; (d) Columnar and dendritic shapes of biliary casts within the intrahepatic and extrahepatic biliary duct system.

Table 1: Results of the nonparametric Mann-Whitney test analysis of HARI

Variables	Group	Cases	Mean	SD	Mean rank	Wilcoxon W	*Z*	*P*
HARI 1	Non-BCS	36	0.6520	0.1021	27	990	−1.263	0.207
	BCS	18	0.6310	0.1102	25			
HARI 2	Non-BCS	36	0.6314	0.1034	29	1062	−4.013	<0.01
	BCS	18	0.6075	0.0935	24			
HARI 3	Non-BCS	36	0.5903	0.0851	31	1134	−5.171	<0.01
	BCS	18	0.5302	0.0752	20			

Results of the nonparametric Mann-Whitney test analysis of HARI, HARI on postoperative weeks 2 and 3, there were statistically significant differences between the non-BCS and the BCS patients. Postoperative HARI was lower, but there was higher incidence of biliary casts complications (P<0.05). HARI 1, HARI 2, HARI 3 was represented as HARI of the first week, the second week and the third week after operation, respectively. SD: Standard deviation; HARI: Hepatic artery resistance index; BCS: Biliary cast syndrome.

Table 2: Results of logistic regression analysis of HARI

Variables	Exp(β)	SE	Wald χ^2	df	*P*	*OR*	95% *CI* for Exp(β)	
							Lower	Upper
Constant	−1.451	0.501	9.036	1	0.003	0.191	–	–
HARI 1	0.262	1.131	0.079	1	0.841	1.300	0.143	12.662
HARI 2	0.201	1.132	0.076	1	0.802	1.223	0.121	12.928
HARI 3	0.636	0.673	5.301	1	0.024	1.889	1.166	7.490

Results of logistic regression analyses of HARI, *OR* of HARI 1, HARI 2, HARI 3 after operation were >1, suggested HARI was possible to an independent risk factor. *OR* of HARI 3 was of statistically significant differences (P<0.05). HARI: Hepatic artery resistance index; BCS: Biliary cast syndrome; SE: Standard error; *OR*: Odds ratio, *CI*: Confidence interval.

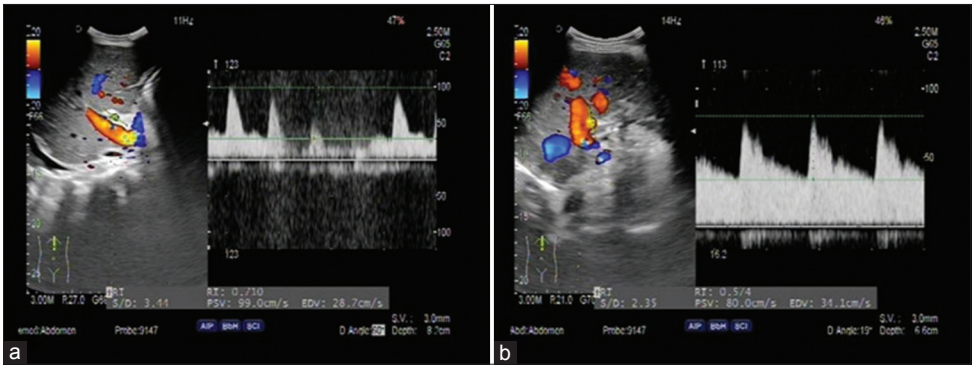

Figure 2: Determination of hepatic artery resistance index (HARI) by color Doppler flow imaging. (a) The right hepatic artery peak systolic velocity (PSV) 99.0 cm/s; end diastolic velocity (EDV) 28.7 cm/s; HARI 0.710; (b) The right hepatic artery PSV 80.0 cm/s; EDV 34.1 cm/s; HARI 0.574.

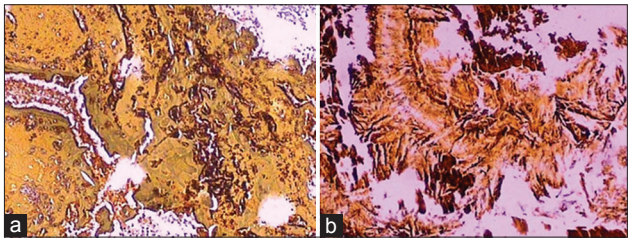

Figure 3: The pathological changes of biliary casts (H and E, original magnification ×100). (a) Biliary casts, bilirubin crystal surrounding the sample structure, hyperplasia of fibrous tissue, micrangium, bile duct epithelial cells were found, inflammatory cells in biliary casts surface; (b) The composition was bilirubin and calcium. By contrast, fibrous tissue, blood vessels, bile duct epithelial cells were not found.

duct complications following OLT gradually becomes an important and hotly debated topic. Due to the influence of the complex diversity of liver transplant procedures by many factors, and the unique arterial blood supply of the anatomy of the biliary system, the capacity for tissue regeneration is low, and the risk factors accounting for postoperative bile duct complications and its mechanism remains poorly understood. It thus becomes a highly restrictive factor when attempting to improve the success rate of liver transplantation. Moreover, there is an urgent need for newer technology to better manage the key problems that are associated with liver transplantation, which represent a specific need for further development.[10]

Biliary casts are composed of necrotic material of the intrahepatic and extrahepatic bile duct after OLT, which forms a biliary tree. Simultaneously, biliary casts might be accompanied by multiple biliary strictures, which

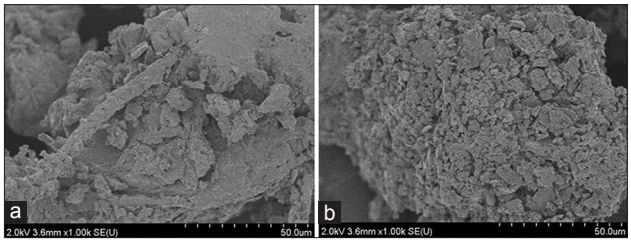

Figure 4: Morphology of biliary casts and bile duct stones by scanning electron microscopy (original magnification ×10,000). (a) A biliary cast was morphologically composed of relatively loose filamentous structures; (b) A bile duct stone was morphologically shaped by dense spherical structures.

are predominantly caused by ITBL.[11] Hepatic arterial anastomotic stricture, hepatic artery thrombosis, or abnormal hepatic artery blood supply deficiency, can all cause ITBL, eventually leading to biliary stricture or bile leakage. Biliary reconstruction that is elected following damage to the bile duct peripheral vascular network can also cause ITBL, bile duct stricture after OLT including anastomotic stenosis, and nonanastomotic strictures (NAS). Accurately, NAS is an ischemic necrosis of the diffuse biliary tree following hepatic arterial thrombosis. In addition, some bile duct strictures might occur in cases where the hepatic artery is unobstructed. Thus, due to this kind of bile duct stricture, the imaging findings are similar to NAS, and consequently, this stricture type is also referred to as ITBL.[12] At present, the pathological mechanism of ITBL remains unclear. However, it is quite well-known that outcomes in ITBL are influenced by the combined action of many kinds of risk factors, which include the following major associating factors including ischemia injury, induced immune damage and bile salt-induced cytotoxic damage.[13] According to our clinical observations, biliary casts generally form at least 1 month after transplantation. The choices of treatment methods of biliary casts are quite varied and includes choledochoscope, ERCP and percutaneous transhepatic cholangiography drainage.[14-16]

Cold ischemic insult induces direct injury to the bile duct cells and damages the arterioles of the peribiliary vascular plexus, which consequently leads to apoptosis and necrosis of bile duct cells.[17] A retrospective review of 355 OLT cases identified that 2.5% of the cases were diagnosed by cholangiography and that the warm ischemic time was significantly longer in BCS patients.[18] Damage to the peribiliary vascular plexus of the bile duct can also result in ITBL under conditions of biliary reconstruction. Blood supply to the biliary tract is predominantly from the arterial system rather than the portal vein system. In addition, hepatic arterial reconstruction is restricted to the biliary tract side in OLT recipients. Thus, the condition of reconstruction of the blood supply from the hepatic artery is an important factor to consider in the case of bile duct complications occurring.[19]

Determination of HARI can be achieved by CDFI, and because of changes in the resistance of the hepatic arterial vascular bed, CDFI is an effective means to determine whether the hepatic artery will stricture. HARI reflects hepatic arterial systolic and diastolic blood flow velocity changes and is not affected by vascular morphology and sampling point. It is thus important to determine the parameters of hepatic arterial blood flow, where the normal value ranges from 0.55 to 0.80. A depressed HARI value indicates that the arterial wall elasticity has declined, and informs proximal blood flow obstruction.

At postoperative weeks 2 and 3, this study found that there were significant differences in the HARI score between patients with BCS and patients without BCS. Logistical regression analysis showed that the *OR* of HARI was >1, which suggested that HARI represented a possible independent risk factor for biliary complications after OLT. According to the results of statistical analysis, we confirmed that an HARI score of 0.64 was the critical value when biliary complications occurred, and the value was within the normal range (0.55–0.80), which suggested that biliary complications were highly sensitive to hepatic arterial ischemia. There have been no characterizations of obstructed hepatic arterial blood supply of the lower is likely to lead to biliary complications.

In liver transplantation, we should closely monitor dynamic changes in the hepatic arterial blood flow, and pay close attention to the HARI value. Maintaining an unobstructed hepatic artery depends on the improvement of anastomosis technology, organ preservation technology and microthrombosis anti-coagulation therapy. It is possible that HARI is an independent risk factor and an early predictive factor for BCS. However, the specific mechanisms underlying bile duct injury require further investigation.

Formation of biliary casts and bile duct stones are similar but not completely the same in terms of their development. Their composition, morphology and microstructure exhibit certain unique differences. Biliary casts and bile duct stones have a similar microstructure, but their forming mechanism is quite different. With morphology, biliary casts appear as columnar and dendritic shapes within the intrahepatic and extrahepatic biliary duct but differ from bile duct stones, and the material quality of biliary casts is often palpably softer. Scanning electron microscopy showed that biliary casts appear in a variety of forms, and biliary casts often appear in the shape of relatively loose filamentous structures, including irregular sheets composed of imbricated accumulations, a porous honeycombs structure and adherent crystalline substances,[20] while bile duct stones take on the appearance of dense spherical structures.

Choledochoscopy procedure showed a large number of flocs in the bile duct system of BCS patients. The pathological changes in biliary casts include the appearance of bilirubin crystals that surround the sample structure, with cellulose, and hyperplastic fibrous tissue, presence of micrangium,

and presence of bile duct epithelial cells, and infiltrating inflammatory cells in biliary cast surfaces. The presence of micro blood vessels and collagen fibers in the biliary casts was related to injury of the bile duct mucosa. The composition of bilirubin and calcium in bile duct stones was evident, and yet fibrous tissue, blood vessels, and bile duct epithelial cells were not found.

We believe that biliary casts represent pathological changes that are caused by multi-factorial events after bile duct injury. BCS was correlated with ITBL following OLT. The occurrence of BCS was associated with bile duct tissue damage, but BCS in itself is not caused by a single pathological factor, and might instead be associated with functional recovery, biliary strictures and obstruction, acute and chronic rejection, recurrent cholangitis, cold and warm ischemia episodes, hepatic ischemia, and reperfusion injury.[18,21-23] BCS is one of the clinical manifestations of bile duct complications that can provoke ITBL following OLT.

During the formation of bile stones, and related to the biliary core factor mucoprotein,[24] both mucoprotein secretion and expression of bile and bile duct tissues, showed a pathological and increasing trend in cholelith disease patients.[25] In the process of liver transplantation, the presence of many strongly induced protein expression species and active substances in the human body are present, and their presence is mostly as a consequence of ischemic factors.[26,27] Biliary stricture can cause rheological changes to the bile, cholestasis, further formation of bile duct deposition, biliary sludge, and crystallization of bile stones.

It is formally possible that HARI might represent independent risk factors and might be an early predictive factor of BCS. In addition, BCS was correlated with ITBL following OLT. Furthermore, biliary casts and bile duct stones with different morphology and components were identified. Cholangiography should be considered as the main approach for diagnosing BCS, and in the treatment of BCS by choledochoscope or duodenoscope.

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