ARTICLE

Pathotyping and Clinical Manifestations of Biliary Cast Syndrome in Patients After an Orthotopic Liver Transplant

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Abstract

***Objectives*: To summarize the pathotyping and clinical manifestations of biliary cast syndrome in patients after an orthotopic liver transplant.**

***Materials and Methods:* The clinical manifestations, auxiliary examination, therapeutic regimen, and clinical efficacy of 103 biliary cast syndrome patients who underwent an orthotopic liver transplant were retrospectively analyzed. Patients were divided into 6 groups from type 1 to type 6, according to the injury level of the biliary duct epithelium.**

***Results:* Many biliary cast syndrome patients showed symptoms including jaundice, dark urine, argillaceous stool, itchy skin, and fever. Serum levels of alanine aminotransferase, γ-glutamyl transpeptidase, alkaline phosphatase, and total bilirubin were increased. In addition, total white cell counts in peripheral blood also were increased. T-tube cholangiography showed filling defects of various amounts. Optical fiber choledochoscope examination revealed that the biliary tract was filled with solid substances, and necrosis of the biliary tract epithelium was observed in some biliary cast syndrome patients. From type 1 to type 6 biliary cast syndrome patients, the probability of clinical symptoms and biliary tract stricture gradually increased, the time needed for supporting gradually prolonged after removal of the biliary cast, and T-tube cholangiography showed that the filling defects gradually expanded.**

***Conclusions:* Clinical manifestations and cholangiography presentations mainly depend on pathotyping.**

Key words: *Liver transplant, Biliary cast, Postoperative complications, Pathotyping, Image manifestation*

Introduction

Complications after a liver transplant include biliary tract complications, vascular complications, infections, and various rejections. Biliary cast syndrome (BCS) is a syndrome that is characterized by the presence of a biliary cast (BC), which causes obstruction of the biliary tree, leading to a series of clinical manifestations; it is simultaneously accompanied by 1 or more nonanastomotic biliary tract epithelial necrosis or stenosis.[1] The precise mechanism of BCS is poorly understood. Biliary cast syndrome cannot be avoided completely; it manifests differently in the clinic, and is difficult to treat, with a poor prognosis, high morbidity, and retransplant rate.

The present study retrospectively analyzed the clinical data of 103 BCS patients who were admitted in the Liver Transplantation Institute in General Hospital of Chinese People's Armed Police Forces between April 2002 and March 2006 in whom we performed pathotyping according to choledochofiberoscopy, thus further recognizing the BCS. In addition, this study analyzed the causes for various clinical manifestations and summarized the treatment methods based on pathotyping in relation with prognosis.

Materials and Methods

General data

Among 650 patients who received a liver transplant at the Liver Transplantation Institute in General Hospital of Chinese People's Armed Police Forces

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from April 2002 to March 2006, fifty-nine patients presented with BCS were recruited into this study. In addition, 44 patients presented with BCS after a liver transplant at other hospitals were concurrently recruited in this study. These 103 patients with BCS after the liver transplant included 91 men and 12 women (mean age, 49.9 y; range, 23-70 y). Of these 103 BCS patients, 19 underwent a piggyback orthotopic liver transplant and 84 underwent standard orthotopic liver transplant. All protocols were approved by the ethics committee of the institution before the study began, and the protocols conformed with the ethical guidelines of the 1975 Helsinki Declaration. Written, informed consent was obtained from all patients.

At the Liver Transplantation Institute, 95% of patients received T-shaped tube placement after the liver transplant; at 2 weeks after the liver transplant, routine cholangiography was performed, followed by occlusion of the T-shaped tube; at 3 months after surgery, a cholangiography was performed again to determine whether T-shaped tube should be extracted.

Immunosuppressive therapy

Before transplant, anti-Tac monoclonal antibody (1 mg/kg) + methylprednisolone (10 mg/kg) were used for immune induction. After transplant, tacrolimus (0.1 mg/kg/d) + mycophenolate mofetil (1500 mg/d) + prednisone acetate tablets (5 mg/d × 90 d) were used as immunosuppressants.

Diagnostic evidence for biliary cast syndrome

Patients were considered to have a greater risk for BCS if all of the following criteria were met: Clinical symptoms: obstructive jaundice (jaundice, dark urine, argillaceous stool, itchy skin), and/or infection of biliary tract (fever, septic shock). Laboratory examinations included increased levels of alanine aminotransferase (ALT), γ-glutamyltransferase (GGT), alkaline phosphatase (ALP), total bilirubin (TBIL), direct bilirubin (DBIL), increased peripheral blood leucocyte counts, and positive pathogenic microorganism cultures. Radiographic examinations included intrahepatic biliary tract filling defect shown by a T-shaped tube cholangiography, endoscopic retrograde cholangiopancreatography, magnetic resonance cholangiopancreatography, or percutaneous transhepatic cholangiography. Cholangiography was used for further examination: Biliary cast syndrome finally would be diagnosed if there are casts causing obstruction of the biliary trees. There are various pathotypes based on biliary tract epithelial injury degrees. Some patients have no clinical symptoms or laboratory index changes, but there were intrahepatic biliary tract filling defects shown by T-shaped tube cholangiography or by endoscopic retrograde cholangiopancreatography, magnetic resonance cholangiopancreatography, and casts that could be observed by using a choledochoscope

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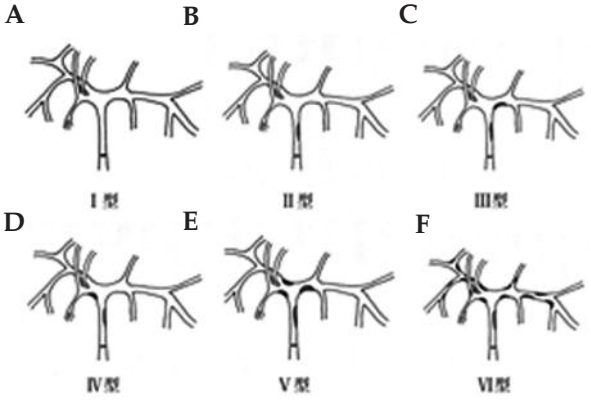
Biliary cast syndrome biliary pathotype

In accordance with the injury levels detected by choledochofiberscope findings, BCS patients were divided into 6 types (Figure 1) as follows: type 1 represents pure BC (with an intact bile duct epithelium); type 2 represents BC formation (with a necrotic common hepatic duct bile duct epithelium); type 3 represents BC formation (with necrotic bile duct epithelial affecting the common hepatic duct and left hepatic duct); type 4 represents BC formation (with the necrotic bile duct epithelium affecting the common hepatic duct and the right hepatic duct); type 5 represents BC formation (with the necrotic biliary duct epithelium affecting the common hepatic duct, and the left and right hepatic duct); and type 6 represents BC formation (where the necrotic biliary duct epithelium affects the common hepatic duct, and the left and right hepatic duct).

Figure 1. Various Forms of the Biliary Cast



(A) Type 1 represents a pure BC (bile duct epithelium is intact); **(B)** type 2 represents BC formation (common hepatic duct bile duct epithelium is necrotic); **(C)** type 3 represents the BC formation (the bile duct epithelial necrosis affects the common hepatic duct and left hepatic duct); **(D)** type 4 represents BC formation (bile duct epithelial necrosis affects the common hepatic duct and right hepatic duct); **(E)** type 5 represents BC formation (biliary duct epithelial necrosis affects the common hepatic duct, both left and right hepatic duct); and **(F)** type 6 represents BC formation (biliary duct epithelial necrosis affects the common hepatic duct, both left and right hepatic duct, and above).

Statistical analyses

Liver function indices of all patients (ALT, GGT, ALP, TBIL, DBIL) were analyzed before treatment, the measurement data are expressed as means ± SD. All patients were followed-up for 12 months. The clinical symptoms, radiographic findings, treatment sessions, and prognoses in each group were taken into consideration. General information and bile culture results of all BC patients were statistically analyzed.

Results

Clinical data of biliary cast syndrome patients

Among 103 BCS patients, 59 cases underwent a liver transplant at our hospital, the incidence rate was 9.1% (59/650), in which 20.6% were in the year two thousand two, 16.5% were in the year two thousand three, 9.9% were in the year two thousand four, and 5.9% were in the year two thousand five. There were 14 cases of type 1, 18 cases of type 2, 27 cases of type 3, 23 cases of type 4, 13 cases of type 5, and 18 cases of type 6. The clinical symptoms, imaging findings, and treatment scheme and outcomes were different among different cases (Tables 1 and 2).

General form of biliary cast

The immediately removed BC was flexible and varied in color, some were solid structures, and some were hollow structures. The dried BC became brittle. The BC forms included "antler shape," "leafless tree" shape, block shape, and sheets (Figure 2). The BC weighed 1 to 70 grams, and their texture varied: while some were soft, some were hard and brittle. There were 71 cases exhibiting leafless tress shape (68.9%), 20 had an antler shape (19.4%), 6 were blocks (5.8%), and 6 were sheets (5.8%); the BC texture was tough in 74 cases (71.8%), hard and brittle in 21 cases (20.4%), and soft in 8 cases (7.8%); and the BC color was black in 38 cases (36.9%), dark brown in 37 cases (35.9%), and light brown in 28 cases (27.2%).

Figure 2. Various Forms of the Biliary Cast

(A) The BC is brown-black in a thin antlershape; **(B)** the BC is yellow-brown in a full antlershape; **(C)** the BC is leafless tree-shaped; **(D)** the BC occasionally exists in the bile duct, and **(E)** after removal, some exist as a stone and some as a bark.

Imaging findings of biliary cast syndrome

There are 4 types of BCS imaging findings (Figure 3): (1) filling defect is seen indistinctly, biliary tree is normal; (2) filling defect is clearly visible, biliary tree is normal; (3) filling defect is dominant, biliary tree is incomplete; (4) only incomplete trunk is seen. The ALT, TBIL, DBIL of type 1 and 2 patients were normal, while the GGT and ALP increased in

Table 1. The Pathotype, Clinical Symptoms, and Radiographic Findings (n)

	Clinical Symptom				Radiographic Findings			
Pathotype	Asymptomatic	Fever	Jaundice	Septic shock	Filling defect is seen indistinctly, biliary tree is normal	Filling defect is clearly visible, biliary tree is normal	Filling defect is dominant, biliary tree is incomplete	Only incomplete trunk is seen
1	14	0	0	0	14	0	0	0
2	18	0	0	0	8	10	0	0
3	11	9	7	0	0	15	12	0
4	8	7	8	0	0	14	9	0
5	0	8	13	0	0	0	10	3
6	0	18	18	1	0	0	9	9
Total	51	42	46	1	22	39	40	12

Table 2. The Pathotype, Treatment Scheme, and Outcomes (n)

Pathotype	Treatment Scheme				Outcomes				
	Biliary Cast Taken Off	Support 3 mo	Support 6 - 12 mo	Long-Term Support	Cured	Improved	Stenosis	Retransplant	Death
1	14	0	0	0	14	0	0	0	0
2	18	0	0	0	18	0	0	0	0
3	27	20	7	0	18	4	5	0	0
4	23	0	23	0	16	4	3	0	0
5	13	0	8	5	0	9	4	0	0
6	18	0	18	0	0	0	18	8	14
Total	103	20	56	5	66	17	30	8	14

Table 3. Liver Function Indices of Patients at Different Pathotypes Before Treatment (Mean ± SD)

Pathotypes	Item				
	ALT (IU/L)	GGT (IU/L)	ALP (IU/L)	TB (μmol/L)	DB (μmol/L)
1 (n=14)	56 ± 6	83 ± 9	132 ± 11	23.6 ± 7.6	10.3 ± 5.4
2 (n=18)	50 ± 8	107 ± 10	143 ± 9	33.6 ± 4.6	8.3 ± 5.4
3 (n=27)	178 ± 24	286 ± 57	223 ± 48	178.7 ± 45.4	119.5 ± 23.7
4 (n=23)	184 ± 22	291 ± 37	195 ± 38	197.6 ± 39.0	109.8 ± 31.7
5 (n=13)	203 ± 24	261 ± 32	309 ± 53	180.6 ± 57.4	124.8 ± 23.4
6 (n=18)	202 ± 44	287 ± 47	332 ± 53	280.6 ± 57.4	194.8 ± 29.5

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; DB, direct bilirubin; GGT, γ-glutamyltransferase; SD, standard deviation; TB, total bilirubin
Normal ranges: ALT, 1-40 IU/L; GGT, 5-54 IU/L; ALP, 15-112 IU/L; TB, 1.7-25.7 μmol/L; DB, 0-8.6 μmol/L

14 patients before treatment (Table 3), no BC and stenosis was found during follow-up. The ALT, TBIL, DBIL, GGT, and ALP increased in 37 type 3 and 4 patients before treatment; mild nonanastomotic stenosis occurred in 5 cases; and 3 cases at 3 to 6 months after giving a support. The ALT, TBIL, DBIL, GGT, and ALP increased in type 5 patients before treatment; and moderate nonanastomotic stenosis occurred in 4 cases at 6 to 12 months after giving a support. The ALT, TBIL, DBIL, GGT, and ALP increased in type 6 patients before treatment; all patients appeared with severe nonanastomotic stenosis during follow-up.

Eight patients exhibited severe necrosis and poor functional recovery (bile secretion < 100 mL/d, hyperbilirubinemia progressively aggravated) within 12 months after the initial liver transplant: 4 cases died of multiple organ failure and poor general conditions in the perioperative period; 3 cases returned to normal after a liver retransplant with no BCS; and 1 case showed a BCS after liver retransplant. The symptoms were relived by choledochofiberscope and support tube treatment. Finally, the BCS disappeared after the third liver transplant in 7 months after the second surgery, postoperative recovery was good. In the remaining 10 cases, 9 cases failed at retransplant because of economic reasons, and all died of multiple organ failure; 1 patient died because of acute obstructive suppurative cholangitis without timely treatment during outside hospital observation. The average survival time was 7.6 months.

Choledochofiberscope findings of the biliary cast syndrome

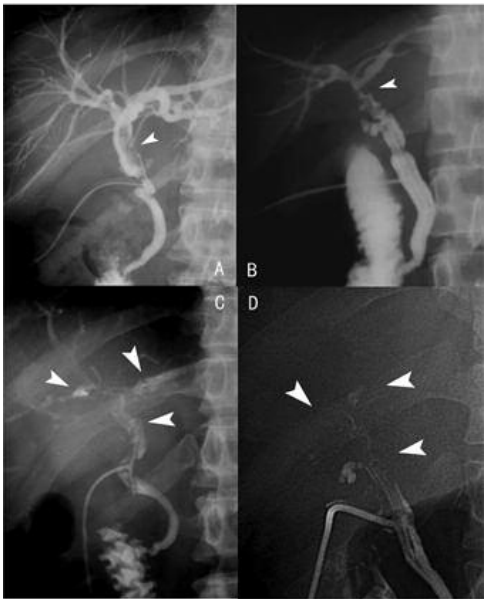
Choledochofiberscope examination was performed 3 months postoperatively. Biliary cast syndrome patients with different pathotypes showed various bile duct walls, mainly biliary epithelial necrosis and emerging granulation tissue, which gradually aggravated from type 1 to type 6 patients (Figures 4 and 5). Biliary cast morphology under choledochofiberscope determined BCS imaging performance (Figure 6).

Prognosis and risk factors

The mortality of BCS patients in this group was 13.6%, and 44.0% after retransplant. Total cure rate was 54%, total improvement rate was 71%, and total stenosis rate was 29%. Bile culture positive rate in BCS patients was 97%. Among the 421 positive strains, there were 94 strains of coagulase-negative staphylococci (22.3%), 84 strains of *Acinetobacter* (20.0%), 77 strains of *Stenotrophomonas maltophilia* (18.3%), 63 strains of *pseudomonas aeruginosa* (15.0%),

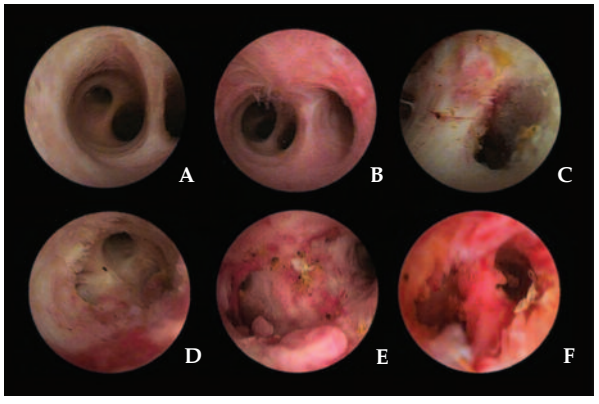
53 strains of *Escherichia coli* (12.6%), 39 strains of *Enterococcus faecium* (9.2%), and 11 strains of *Staphylococcus aureus* (2.6%).

Figure 3. Imaging Findings of the Biliary Cast Syndrome



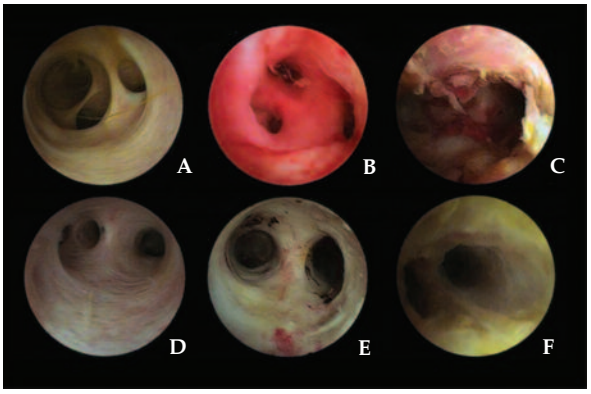
(A) Sparse BC indirect images can be observed within the common hepatic duct, the bile duct wall is smooth; **(B)** the filling defect is clearly visible in the left hepatic duct, the bile duct wall is mostly smooth; **(C)** contours of the biliary tree are outlined but are incomplete; and **(D)** the biliary tree cannot be observed, the trunk is visible. White arrows refer to the BC.

Figure 4. Bile Duct Wall of Various Pathotypes Patients With the Biliary Cast Syndrome After Biliary Cast Removal Under Endoscope



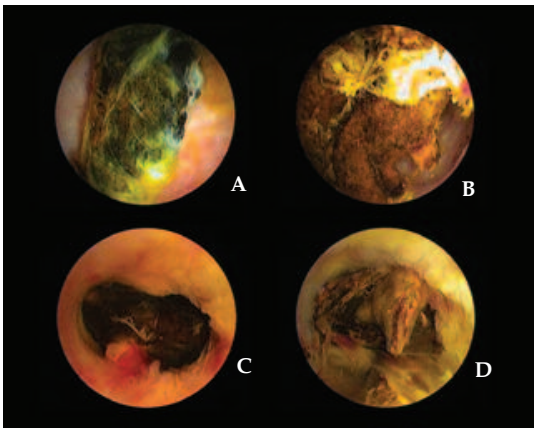
(A) Type 1: the biliary epithelium is intact; **(B)** type 2: the common hepatic duct biliary epithelial regional necrosis, and epithelial congestion around the necrotic area are visible; **(C)** type 3: biliary epithelial necrosis involves the common and left hepatic duct, the bile duct wall lost normal color, only regional congestion area is visible; **(D)** type 4: biliary epithelial necrosis involves the common and right hepatic duct, granulation tissue covered after the bile duct epithelium fell off, the biliary epithelium above necrosis area is normal; **(E)** type 5: epithelial necrosis involves the common, left, and right hepatic duct; the epithelium is replaced by granulation tissue and some break into the lumen; and **(F)** type 6: biliary epithelial necrosis involves the common, left, and right hepatic duct and above; massive necrotic tissue and granulation tissue break into the lumen, and cannot be visualized under the endoscope.

Figure 5. Endoscopic Biliary Duct Wall in a Healthy Human Versus Patients With the Biliary Cast Symptom After Removing the Biliary Cast



(A) Normal bile duct epithelium is intact, color is pale pink, wall is smooth, ridge between the lumen is thin; **(B)** type 5 patients with BC symptoms show that the biliary wall necrotic tissue completely fell off and is replaced by scar tissue, a smaller bile duct lumen opening becomes narrower, the ridge between the lumen is thicker at 6 months after choledochoscopic treatment; **(C)** in some type 5 patients with BC symptoms after choledochoscopy treatment, hyperplasia is seen in the granulation tissue of necrotic areas growing into the lumen, which may be associated with the stimuli of long-term support tube; **(D)** the epithelium is intact in type 1 patients with BC symptom; colors appear pale pink, the wall is smooth, but the ridge between the lumen is thicker than in a healthy human; **(E)** type 2 patients with BC symptoms show that the bile duct lumen becomes smaller, the ridge between the lumen is thicker than in a healthy human; and **(F)** necrotic areas of type 5 patients with BCS are replaced by scar tissue, bile the duct wall color is pale and the opening is smaller when rechecked; it is not visualized under endoscopy.

Figure 6. Imaging Performance of the Biliary Cast Syndrome Determined by the Biliary Cast Under Choledochofiberoscopy



(A) The BC floats in the common hepatic duct, bile duct wall is smooth, so imaging findings are sparse and barely visible, rather than filling defect; **(B)** the BC occupies most of the bile duct, resulting in filling defect visible at 1 side of the bile duct, the bile duct is mainly smooth; **(C)** the BC fills most of the bile duct, thus the contour of the biliary tree can be outlined but incomplete; and **(D)** the BC blocks the bile duct completely, it cannot be detected under choledochofiberoscopy; therefore, the biliary tree trunk cannot be visualized, only the trunk is observed.

Data of 59 BCS patients admitted to our hospital were systematically analyzed, risk factors include ischemia-reperfusion injury in 20 cases (33.9%), prolonged cold preservation in 21 cases (35.6%),

prolonged warm ischemia in 19 patients (32.2%), hepatic artery thrombosis in 7 patients (11.9%), contrast agent stimulation in 14 cases (23.7%), splenic artery steal in 1 case (1.7%), University of Wisconsin solution flushing of the bile duct in 1 case (1.7%), and technical factors in 10 cases (16.9%). In addition to splenic artery steal as the recipient factor and technical factors as the iatrogenic factors, other factors are the donor liver factors, while *cytomegalovirus* infection factors remained unclear.

The involved 7 patients with hepatic artery embolism were treated with alprostadil, dextran-40, and heparin; 4 cases were found to have arterial frequency spectrum by color Doppler ultrasound 10 days after the diagnosis, and there was no nonanastomotic stoma stenosis in the biliary duct during follow-ups. One case appeared with a liver abscess in the right liver lobe that was healed with percutaneous puncture and draining. In addition, 3 cases presented with diffuse biliary tract necrosis and stenosis; unfortunately, they died of liver functional failure before the secondary liver transplant. Several studies have already described biliary tract casting, so we did not perform repeat research.

Discussion

Mechanism underlying the biliary cast formation

Biliary cast consists of bilirubin 10% to 50% and 5% to 10% protein, but bile salt and cholesterol are rare.[2] Biliary cast formation may contribute to exudative inflammation of bile duct epithelium.[1,3,4] Many factors have been reported to result in biliary epithelial injury.[2,5-12] Bile duct epithelium appears as exudative inflammation under inflammatory cytokine stimulation; fibrin diffusely or locally deposits in the bile duct, then degenerates and fixes after combining with bile to form BC skeleton. Bilirubin deposits and forms BC taking some components of the skeleton as the core; a hollow structure will occur if deposition is incomplete. Biliary cast formation may obstruct bile duct and result in severe jaundice. Biliary cast coinfection contributes to acute obstructive suppurative cholangitis.

Relation of hepatic artery thrombosis and stenosis with biliary cast syndrome

Transcatheter arterial thrombosis directly results in intrahepatic biliary ischemia, and even diffused biliary necrosis and stenosis, which are characteristics of type 6. Hepatic arterial thrombosis is not the only cause of diffused biliary necrosis among the 18 type 6 cases;14 cases were not confirmed to have a diagnosis of hepatic arterial thrombosis. Even after treatment, diffuse biliary necrosis and stenosis were not present; among the 7 analyzed cases of hepatic artery thrombosis, 4 occurred during arterial reconstruction with no presence of diffused biliary necrosis and stenosis.

Clinical manifestations of different pathotypes of the biliary cast syndrome

Bile duct epithelial injury involves mostly the bile duct full-thickness wall, and the patient outcome is associated with the location and scope of biliary epithelial necrosis, by which this group of patients was classified. Type 1: the mildest pathotype; type 2: often found in the examination, BC in type 1 and type 2 is multiple, the color is dark, "sheet-"or "block-shaped," seldom "antler-shaped," and weighing 1 to 25 grams. These 2 types were asymptomatic because the biliary epithelium is repaired, or mild stenosis had not affected drainage of bile. Type 3: biliary epithelial necrosis involves the common and left hepatic duct; type 4: involves the right lobe of liver is more crucial than the left lobe in liver function so type 4 pathotype is more serious than type 3; the occurrence of these 2 types of symptoms depends on the BC nature and quantity. Most patients are asymptomatic, some patients show symptoms owing to BC and biliary stricture affecting bile drainage or infection. There are 33.4% and 30.4% patients at these 2 types showing fever, 25.9 % and 34.8% having jaundice; all needed early post-operative intervention.[13] Types 3 and 4 of the BC is mostly yellow brown with some dark; the BC shape is mostly the antler or leafless tree branch, some as leafless tree trunk, weighing 10 to 47 grams. Type 5: biliary epithelial necrosis extends because the bile drains into 2 hepatic lobes; this is more serious in type 5 than in types 3 and 4. The symptoms are apparent in the early postoperative period and require early intervention as well as long-term support tube after the removal of the BC. Type 6: the bile duct epithelial injury reaches a peak range and influences all bile drainage. The symptoms are apparent during the early postoperative period and require an intervention to circumvent the crisis. A retransplant is suggested if the time permits. The BC

is mostly yellow brown, some are brittle, weighing 30 to 70 grams.

Biliary cast syndrome diagnostic criteria

Types 1 and 2, the biliary tree is full and intact by visualization because of mild biliary epithelial injury. Types 3 and 4: the bile duct epithelial injury aggravates, so more biliary trees are incomplete and only outlined. Types 5 and 6: the bile duct epithelium is greatly damaged, the formed BC and necrosis floss fill in the bile duct; a complete profile cannot be displayed by contrast, only the residual trunk is visible. Cholangiography is believed to be the criterion standard for BC diagnosis,[14,15] showing the filling defect of the biliary tree. In addition, potential BC characters in biliary duct can be estimated. A small number of filling defects is actually floating floc in the clinic, and radiography is unable to confirm the necrotic severity of the biliary epithelium. Choledochofiberscope makes up for the shortcomings of cholangiography, and fully explains the radiographic findings obtained. Choledochofiberscope is a potential criterion standard for BCS diagnosis, clinical symptoms serve as an additional diagnostic criteria.

Biliary cast syndrome prognosis

Types 1 and 2 bile duct epithelial injury are mild, and all of our patients were cured. Type 5 patients with severe biliary epithelial injury can relieve symptoms after active conservative treatment and their quality of life improves. To avoid retransplant, owing to a broad range of necrosis, the GGT and ALP are high for a long time. Type 6 has serious biliary epithelial injury and is not self-cured, massive sphacelus obstructing the bile duct cannot be cleared, thus the need for a retransplant. Type 3 and 4 can achieve similar efficacy after active treatment, as type 1 and 2, otherwise the disease will progress. A transplant center has reported 45% (36 out of 80 patients) are candidates for liver retransplant because of biliary complications.[16] Although symptoms can be relieved, even reoperation can be avoided in some patients by improving access to organs and minimally invasive methods;[17-23] 30% to 50% of the diffuse duct stenosis or intrahepatic bile duct stenosis patients require a retransplant or they die of complications.[24,25] The mortality in this group of BCS patients was 13.6%, and the retransplant mortality rate was 44.0%, which demonstrates its seriousness.

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