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Original Article

Clinicopathological features and post-resection outcomes of biliary cystadenoma and cystadenocarcinoma of the liver

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Backgrounds/Aims: Biliary cystadenoma (BCA) and biliary cystadenocarcinoma (BCAC) account for 5%-10% of liver cystic diseases. In this study, we analysed the clinical presentation and surgical management of patients with BCA and BCAC. **Methods:** We retrospectively analysed the medical records of 23 BCA and 7 BCAC cases diagnosed between January 2007 and December 2013. **Results:** There was a statistically significant difference in age (p=0.044) and sex (p=0.048) between BCA and BCAC groups. In the BCA group, 17 patients showed no symptoms (74%), 5 had abdominal pain (22%) and 1 showed abdominal distension (4%). In the BCAC group, two patients were without any symptoms (29%), three had abdominal pain (43%), one showed abdominal distension (14%) and one had fever and chills (14%). The cystic lesion size was widely variable; thus, there was no statistical difference (p=0.84). Complete resection was performed in all patients with BCA and BCAC. No tumour recurrence developed in patients with BCA. In patients with BCAC, 1-, 3- and 5-year disease-free survival rates were 100%, 85.7% and 57.1%, respectively, and 1-, 3- and 5-year overall patient survival rates were 100%, 100% and 75.0%, respectively. **Conclusions:** It is difficult to distinguish between BCA and BCAC via clinical manifestations and diagnostic imaging findings. Surgical resection is the treatment of choice for BCA and BCAC, and patient prognosis after complete resection was very favourable. **(Ann Hepatobiliary Pancreat Surg 2017;21:107-113)**

Key Words: Cholangiocarcinoma; Resection; Bile duct; Malignant change; Premalignant lesion

INTRODUCTION

Biliary cystadenoma (BCA) and biliary cystadenocarcinoma (BCAC) are rare diseases that account for only 5%-10% of all intrahepatic cystic lesions of bile duct origin.[1,2] Advances in diagnostic technology, especially development of cross-sectional imaging modalities, have made it easier to detect these biliary cystic tumours (BCTs).

Although there have been sporadic publications since BCA and BCAC were first reported by Heuter in 1887, it has not been actively studied to determine accurate pathophysiology, survival rate and recurrence rate due to the rareness of these diseases. Despite its rarity, the management of BCTs is important because these lesions are believed to be premalignant and may have a risk of malignant transformation as high as 20%-30%.[3]

In the present study, we investigated the clinical presentation and surgical management of patients with BCA and BCAC. We intended to assess the clinical and radiological characteristics of BCA and BCAC and analyse their post-resection outcomes.

MATERIALS AND METHODS

We retrospectively reviewed the clinical courses of BCT patients at our institution from January 2007 to December 2013. Clinical information, including age, sex, clinical manifestation, tumour marker and liver function tests, radiological features and pathological results were collected. They were followed up until the end of September 2016. This retrospective observational study was approved by the institutional review board of the Asan Medical Center and was performed in accordance

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with the ethical standards laid down in the Declaration of Helsinki.

The routine preoperative evaluation for primary liver tumours has been described in detail elsewhere.[4,5] The volume of cystic tumours was measured using computed tomography (CT) volumetry. The preoperative diagnosis of BCA and BCAC was made based on radiological findings. Important radiological features were the presence of multilobular or unilobular mass with well-defined capsule and presence of one or more of the following structures exhibiting contrast enhancement: papillary projections, internal septation with nodular areas, wall thickness irregularities and mural nodules and coarse calcification along the wall. The postoperative diagnosis of BCT was confirmed by pathological diagnosis after operation.

Data with normal distribution are reported as the mean with standard deviation. Variables not normally distributed are presented as the median with range. Continuous variables were compared using the Student's *t*-test if normally distributed; otherwise, the Mann–Whitney U test was used. Categorical variables were compared using the chi-squared test. Overall and disease-free survival rates were estimated using the Kaplan–Meier method and compared using log-rank tests. Data were considered statistically significant at $p<0.05$. Statistical analyses were conducted using SPSS version 22 for Windows (SPSS, Chicago, IL, USA).

RESULTS

Clinicopathological features of patients with BCT

The BCA group consisted of 23 patients (22 females and 1 male), with a median age of 60 (range: 38-84) years. The BCAC group consisted of 7 patients (5 females and 2 males), with a median age of 68 (range: 51-74) years. There was a statistically significant difference in age (p=0.044) and sex (p=0.048) between the groups.

In the BCA group, 17 patients showed no symptoms (74%), 5 experienced abdominal pain (22%) and 1 showed abdominal distension (4%). In the BCAC group, 2 patients showed no symptoms (29%), 3 experienced abdominal pain (43%), 1 showed abdominal distension (14%) and 1 had fever and chills (14%) (Table 1).

In the BCA group, 15 patients were diagnosed with BCA and 8 with benign cyst on imaging studies, including CT, magnetic resonance imaging (MRI) and ultrasonography.

Table 1. Profiles of patients with intrahepatic biliary cystic tumours

	Biliary cystadenoma group (n=23)	Biliary cystadenocarcinoma group (n=7)	*p*-value
Age (years)	60 (38-84)	68 (51-74)	0.044
Sex (Male:Female) (n)	1:22	2:5	0.048
Symptoms (n)			
Abdominal pain	5	3	
Abdominal distension	1	1	
Fever and chills	0	1	
Absence of clinical symptoms	17	2	
Preoperative diagnosis			
Cystadenoma	15	1	
Cystadenocarcinoma	0	4	
Hepatic cyst	8	0	
IPMN	0	2	
Preoperative laboratory findings			
CA19-9 (U/mL)	15.04±13.74	13.08±8.89	0.20
CEA (ng/mL)	1.23±0.61	1.35±0.51	0.63
AFP (μg/L)	2.56±2.34	2.09±2.35	0.68
AST (IU/L)	22.91±11.52	25.14±7.22	0.55
ALT (IU/L)	17.04±11.71	33.71±15.48	0.03
TBil (mg/dL)	0.79±0.25	0.96±0.54	0.45
γ-GT (IU/L)	31.48±41.24	76.57±64.32	0.035
ALP (IU/L)	63.09±25.96	103.57±58.12	0.013

IPMN, intraducalpapillary mucinous neoplasm; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; AFP, α-fetoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TBil, total bilirubin; γ-GT, γ-glutamyl transferase; ALP, alkaline phosphatase

In the BCAC group, one patient was diagnosed with BCA, four with BCAC and two with intrahepatic papillary mucinous neoplasm. There was no statistically significant difference in the preoperative blood levels of carbohydrate antigen 19-9 (CA19-9; p=0.20), carcinoembryonic antigen (CEA; p=0.63) or α-fetoprotein (AFP; p=0.68) between the BCA and BCAC groups (Table 1). Only one patient in the BCA group had AFP level higher than normal

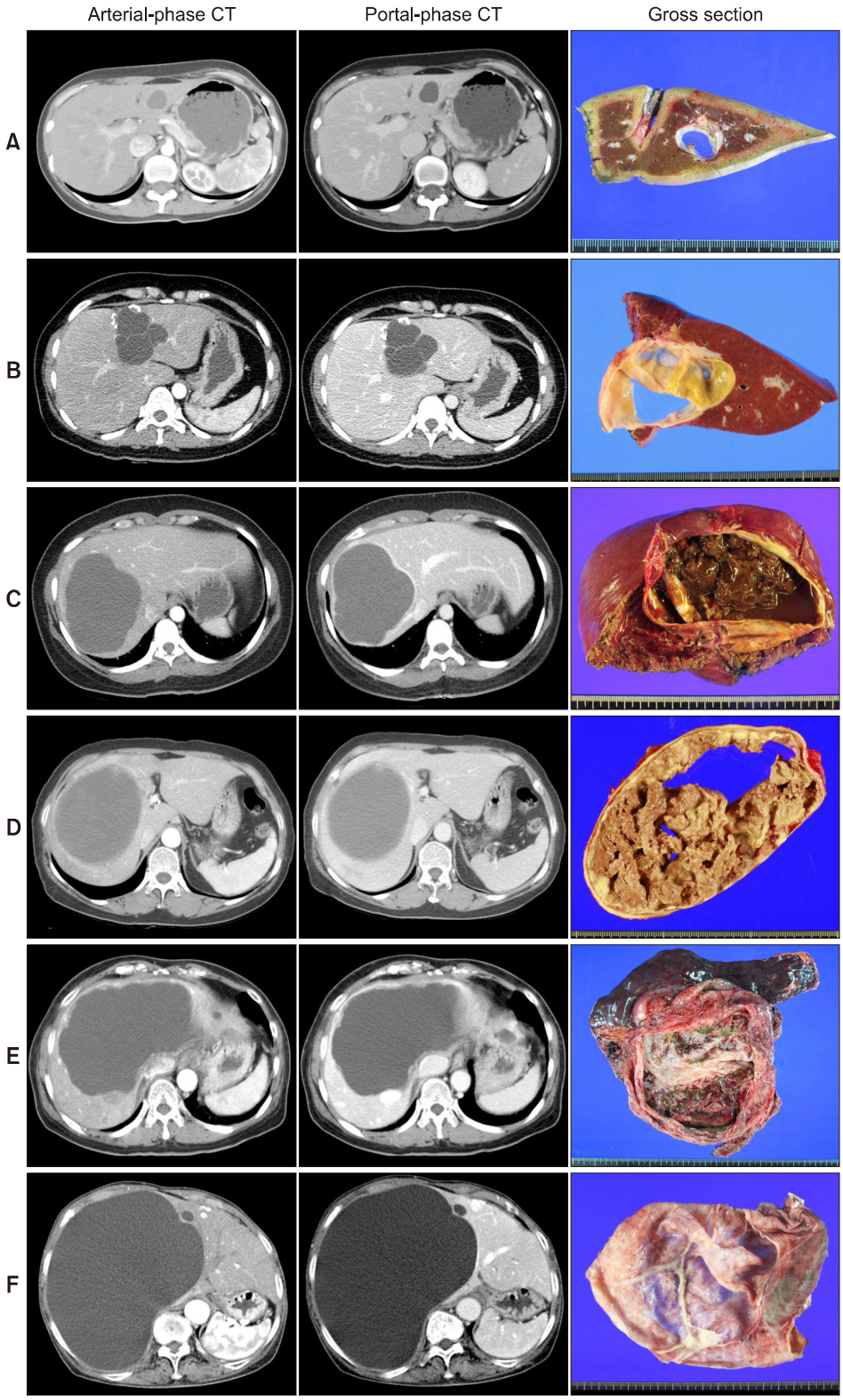

Fig. 1. Preoperative computed tomography (CT) findings and gross photographs of the surgical specimens in patients with intrahepatic biliary cystadenoma. (A) A 3 cm-sized cyst is located in the left liver; (B) a 5 cm-sized multilocular cystic lesion with calcification and fat component is located in the left medial section; (C) a 12 cm-sized unilocular cyst with old haemorrhage and foreign body reaction is located in the right liver; (D) a 13 cm-sized unilocular cyst with extensive erosion and degeneration is located in the right liver; (E) a 15 cm-sized large unilocular cyst is located in the centre of the liver; and (F) a 19 cm-sized huge unilocular cyst is located in the right liver.

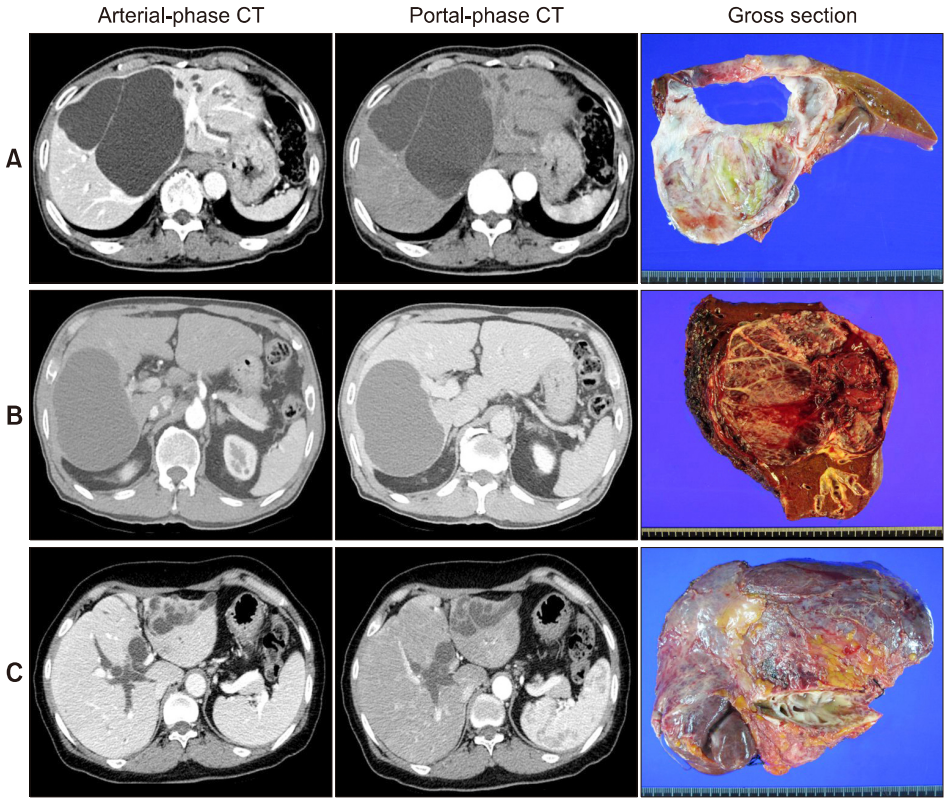

Fig. 2. Preoperative computed tomography (CT) findings and gross photographs of the surgical specimens in patients with intrahepatic biliary cystadenocarcinoma. (A) A 12 cm-sized cyst with multiple septae and friable polypoid mass is located in the medial section; (B) a 12 cm-sized unilocular cystic lesion with multifocal polypoid nodules is located in the right liver; and (C) a 4 cm-sized cystic mass of mucinous type is located in the left liver. This lesion is connected with the left hepatic duct, resulting in diffuse dilatation of the biliary system.

range, and no patient in the BCAC group had elevated AFP level. Six patients in the BCA group and two in the BCAC group had elevated CA19-9.

One patient in the BCA group and no patient in the BCAC group had elevated aspartate aminotransferase (AST). Two patients in the BCA group and one in the BCA group had elevated alanine aminotransferase (ALT). Two patients in the BCA group and two in the BCAC group had elevated total bilirubin. There were no statistically significant differences in the levels of AST (p=0.55) and total bilirubin (p=0.45) between the groups. However, ALT (p=0.030), γ-glutamyl transferase (γ-GT; p=0.035) and alkaline phosphatase (ALP; p=0.013) levels were significantly different between the groups.

Although most patients underwent ultrasonography (18/30, 60%), additional CT was obtained in all patients (100%), whereas fewer patients underwent CT and MRI (13/30, 43%) or CT and MRI with endoscopic retrograde cholangiography (5/30, 17%). In the BCA group, 8 patients had simple cyst on radiological findings and 15 patients had multiseptated cyst. A solid component in the cyst was not observed in the BCA group (Fig. 1). BCAC patients had multifocality (6/7, 86%) and septum formation (5/7, 71%), biliary ductal dilatation (5/7, 71%) or calcification (1/7, 14%) on radiological findings (Fig. 2).

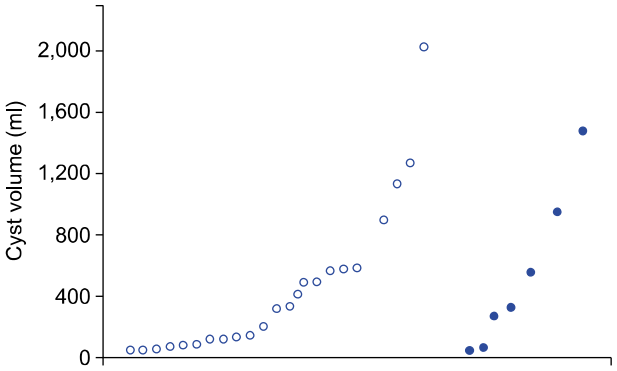

Fig. 3. Distribution of cystic tumour volume according to computed tomography volumetry. Blank circles indicate biliary cystadenoma cases and solid circles indicate biliary cystadenocarcinoma cases.

The volume of cystic lesions was widely distributed from 6 ml to 2,020 ml (Fig. 3), and there was no statistically significant difference in tumour size between BCA and BCAC groups (p=0.84). In the BCA group, 10 patients (43%) had tumours in the left lobe of the liver, and 13 (57%) in the right lobe of the liver. In the BCAC group, five patients (71%) had tumours in the left lobe,

and two (29%) in the right lobe (p=0.39) (Table 2).

Survival outcome of patients with BCT

For the BCA group, the mean follow-up period was 60.8±32.9 months. There was no recurrence of the disease among the BCA group patients during the follow-up period.

For the BCAC group, the mean follow-up period was 65.6±32.4 months. Two patients showed tumour recurrence at both 6 and 12 months after operation, and their 1-, 3- and 5-year disease-free survival rates were 100%, 85.7% and 57.1%, respectively (Fig. 4A). One patient showed recurrence in the lymph node around the proper hepatic artery and superior mesenteric artery at 12 months after operation and died 14 months postoperatively. The other patient showed recurrence in the lung 6 months after operation; thus, he underwent pulmonary metastasectomy and chemotherapy. He has been doing well for 6 years after the metastasectomy (Table 3). Only one patient died at 14 months during the follow-up period; thus, their 1-, 3- and 5-year disease-free survival rates were 100%, 100% and 75.0%, respectively (Fig. 4B).

Table 2. Preoperative imaging and perioperative outcomes of intrahepatic biliary cystic tumours

	Biliary cystadenoma group (n=23)	Biliary cystadenocarcinoma group (n=7)
Preoperative image modality		
CT only	4	2
CT+USG	5	1
CT+MRI	3	1
CT+USG+MRI	8	1
CT+USG+MRI+ERC	3	2
Tumour location		
Right lobe	13	2
Left lobe	10	5
Operation		
Cyst excision	2	0
Partial hepatectomy	4	**0**
Left hepatectomy	8	**3**
Left hepatectomy+S1	1	**1**
Left trisectionectomy	0	**1**
Right hepatectomy	4	**0**
Right hepatectomy+S1	0	1
Right anterior sectionectomy	2	0
Right posterior sectionectomy	2	1

CT, computed tomography; MRI, magnetic resonance imaging; USG, ultrasonography; ERC, endoscopic retrograde cholangiography; S1, caudate lobe resection

DISCUSSION

BCA and BCAC are rare intrahepatic cystic neoplasms of bile duct origin. Although the incidence of BCA is less than 5% of all hepatic biliary cystic lesions,[1,6] this disease should be interpreted with caution due to the lack of reliable criteria for diagnosis. Clinical manifestations of these neoplasms are variable and non-specific. Many of these

Table 3. Pathological findings of the patients with intrahepatic biliary cystic tumours

	Biliary cystadenoma group (n=23)	Biliary cystadenocarcinoma group (n=7)
Periductaltissue invasion (n)	0	2
Lymphovascular invasion (n)	0	0
Perineural invasion (n)	0	0

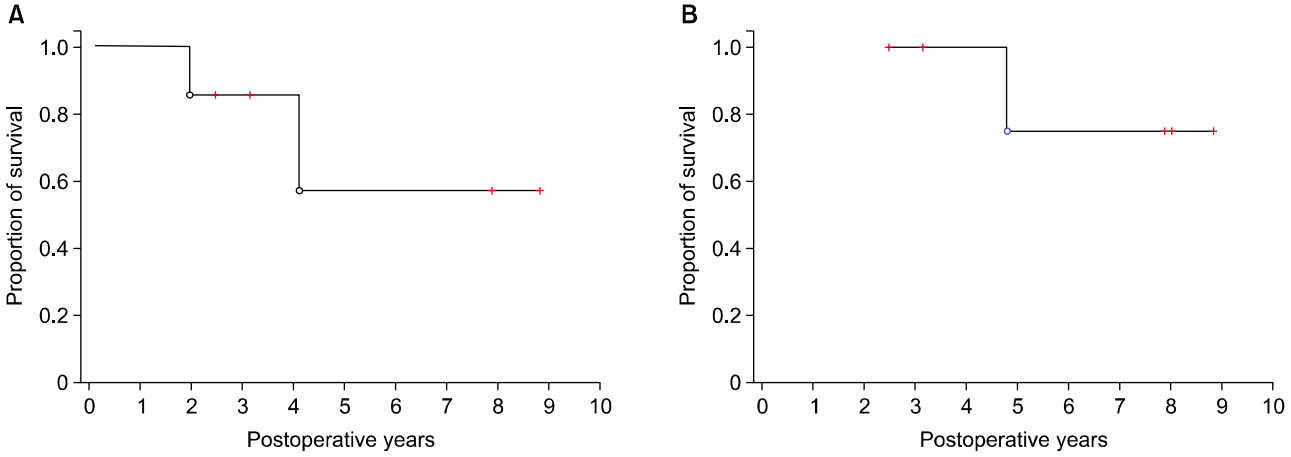

Fig. 4. Disease-free (A) and overall (B) patient survival curves of patients with intrahepatic biliary cystadenocarcinoma.

patients were asymptomatic. The most typical symptoms were abdominal distension, abdominal pain and abdominal mass.[7-9] In the present study, 17 patients in the BCA group were asymptomatic, in whom abdominal pain and distension subsequently occurred. In the BCAC group, the most common symptoms were abdominal pain, abdominal mass and epigastric discomfort, followed by fever and chills. BCA predominantly occurs in females (nearly 90%), but BCAC is more evenly distributed between men and women.[10,11] In the present study, 96% of BCA and 71% of BCAC occurred in women, which is consistent with the findings of other studies.

With development in abdominal imaging technology, hepatic cystic neoplasms are now being discovered more frequently. BCA and BCAC commonly appear as large, solitary, unilocular or multilocular cystic neoplasms with internal septa and well-circumscribed smooth margins on CT and MRI.[12-14] However, it is difficult to practically distinguish between BCA and BCAC using conventional image modalities, such as CT, ultrasonography and MRI. The presence of a septum with nodularity or mural nodules is known to indicate BCAC. Calcifications along the wall and internal septum are uncommon, but the presence of calcification is suggestive of BCAC.[15,16] In the present study, calcification was identified in one case each in BCA and BCAC. Radiological imaging findings may play only a minor role in the differential diagnosis.

There was a statistically difference between the BCA and BCAC group for ALT, γ-GT and ALP. This is probably due to BCAC causing biliary dilatation following biliary obstruction. Horsmans et al.[17] reported normal blood levels of CEA and AFP in patients with BCA or BCAC, suggesting that CA19-9 is important for the preoperative diagnosis of these lesions. Only one patient had elevated AFP and no patients had elevated CEA in our study, but 8 patients (27%) had elevated CA19-9.

Treatment of BCTs must be surgical resection whenever possible due to a potential malignant degeneration of these lesions.[18,19] In the present study, all patients received surgical resection including liver resection or complete cyst excision. Many investigations, including this study, showed that post-resection prognosis of BCA and BCAC is very favourable if complete surgical resection (R0 resection) is performed.[20,21]

Our current analysis has a couple limitations. First, this was a retrospective, single-centre study with a small sample size. Hence, multi-centre studies are still needed to collect additional data on rarely diagnosed cases. Second, the follow-up period of BCAC patients was not sufficiently long for reliable evaluation of the lifelong risk of tumour recurrence.

In conclusion, BCA and BCAC are rare cystic neoplasms of the liver. It is difficult to distinguish between BCA and BCAC using clinical manifestations and diagnostic imaging findings. Surgical resection is the treatment of choice for both BCA and BCAC, and their prognosis after complete resection was very favourable.

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