

Original Article

Biliary Cystadenoma: A Rare Entity of Common Misdiagnosis - An Institutional Experience

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ABSTRACT

Background: Biliary cystadenomas are rare benign neoplasm of the liver with a few hundred cases being reported all over the world. We herein report a series of 12 cases stressing on the importance of imaging and surgery in the management of this rare entity which is often misdiagnosed.

Materials and Methods: Records of 12 patients who underwent surgery for biliary cystadenomas between January 2010 to October 2017, were reviewed retrospectively.

Results: All the 12 patients in the were females with a median age of presentation of 36 (20-55) years. The most frequent symptom was abdominal pain (100%). 4 patients were misdiagnosed as hydatid cyst and one as simple cyst of liver. These were operated elsewhere and presented with recurrence after a median period of 6 months. Liver resection was performed in 8 patients and enucleation in other 4. No recurrence was reported during the follow-up period ranging from 3 months to 7 years.

Conclusion: Biliary cystadenoma closely mimics other cystic space occupying lesions (SOL) of liver and needs to be differentiated from the same, as the treatment varies. Hepatic resection or enucleation of the cyst is the recommended treatment.

KEYWORDS: Biliary Cystadenoma, Complete Resection, Enucleation.

Introduction

Biliary cystadenomas (BCA) are rare cystic neoplasms of the liver. These account for less than 5% of nonparasitic cysts of the liver¹ and occur almost exclusively in middle-aged women. The size ranges from 1.5 to 35 cm.^{2,3}

Other cystic lesions such as simple cysts, hydatid cysts, abscesses, hematomas, cystic metastases, and polycystic liver disease can often have a similar presentation that could probably explain a high likelihood of misdiagnosis.

Biliary cystadenomas were first described in 1943⁴, and only a few hundred cases have been reported in the literature to date. These are usually benign lesions with the potential for malignant transformation.^{3,5,6} Developmentally, these may arise from either an aberrant bile duct or directly from a primitive hepatobiliary stem cell.^{1,7,8} The majority are intrahepatic (85%)^{6,7,9,10,11}, few are extra hepatic^{5,7,12}, and rarely the origin may be from the gall bladder.^{9,10,12}

The real challenge is to identify these lesions accurately in the preoperative setting as they closely mimic other cystic lesions of the liver, and the treatment varies in these various lesions. Classical features of biliary cystadenoma like enhancing septae or mural nodules are present only in a third of the patients. Moreover, preoperative imaging is inconclusive in differentiating between the benign form from the malignant form; hence these lesions should always be resected. The dilemma does not end here, as it is impossible to reliably distinguish a simple cyst or a hydatid cyst from a benign biliary cystadenoma intraoperatively. Such suspicious lesions are often subjected to deroofing, marsupialization, or partial resection that lead to a high rate of recurrence (>90%). A high index of suspicion is required in these situations. Preoperative imaging indicative of biliary cystadenoma, absence of daughter cysts, clear fluid within the cyst, and intraoperative frozen section from the wall of the cyst can help in deciding the extent of resection in such situations. Resection or enucleation of the cyst is the treatment of choice whenever biliary cystadenoma cannot be ruled out conclusively during intraoperative evaluation.

The present case series aims to emphasize the significance of radiological features in preoperative diagnosis of biliary cystadenomas, surgical management, and postoperative follow-up for recurrence.

Materials and Methods

After permission from the Institutional Ethical Committee, records of patients with biopsy-proven biliary cystadenomas treated between January 2010 and October 2017 at our institute were reviewed retrospectively. Patient records were reviewed for demographic characteristics, clinical presentation, radiological findings, past and present

surgical details, and outcome of surgery in terms of morbidity and mortality. Preoperative diagnosis was based on the presence of one or more radiological findings using ultrasound or cross sectional imaging: internal septations, mural nodules, papillary projections, and cyst wall enhancement. The choice of surgical procedure was based on the site of the lesion and proximity to the hepatic hilum and major vessels. Liver resection was the preferred procedure, and enucleation was done when resection was not feasible due to proximity to hilum or major vessels. Postoperative complications and morbidity were recorded. Histopathological diagnosis of biliary cystadenoma was confirmed in all patients. Patients were screened for recurrence by ultrasound abdomen. Quantitative data was reported as median with range, and binomial data as percentages.

Results

There were a total of 12 patients in the study, all of them being female. The median age of presentation was 38 years (Range: 20-55 years). The most common symptom was abdominal pain (100%), followed by abdominal fullness and abdominal mass (**Table 1**). One patient had jaundice preoperatively due to tumor emboli in the left hepatic duct. The median duration of symptoms was 13 months (2-24 months).

Recurrent Cases and Interventions

Five patients had index surgery done elsewhere, in the form of deroofing of cyst for suspected hydatid cyst in four

Table 1: Clinical and radiological characteristics.

	Characteristic	n (%), N=12
Symptoms	Pain abdomen	12(100%)
	Abdominal fullness	4(33%)
	Abdominal mass	4(33%)
	Previous surgery	5(41%)
Radiological findings	Multiloculated	12(100%)
	Internal septations	12(100%)
	Papillary projection	4 (33%)
	Enhancing septa	6 (50%)
	Mural nodules	3 (25%)

patients, and one patient had undergone cystojejunostomy for suspected simple cyst of the liver. All had a recurrence, which occurred in 3 patients within 6 months and in 2 patients after 6 months of the index surgery (median: 7 months (2-10 months)) Only one patient with recurrent giant cystadenoma had intervention in the form of percutaneous cyst fluid aspiration before the definitive surgery. Two patients in the recurrence group had cyst wall biopsy done during the initial surgery, which was reported as biliary cystadenoma. The interval between the diagnosis of recurrence to the definitive procedure varied from 1 to 3 months.

Routine blood investigations, including liver function tests and coagulation parameters, were within normal limits in all patients except one patient who had obstructive jaundice due to tumor emboli in the left hepatic duct. Serum carbohydrate antigen 19-9 (CA 19-9) was raised preoperatively in three patients (25%). Preoperative diagnosis was based on typical ultrasound and CECT findings that included one or more features like a multiloculated cyst with a well-defined capsule, internal septations, mural nodules, and solid papillary projections. (Table 1). Differential diagnosis of biliary cystadenoma was reported by the radiologists in 5 out of 7 (71.4%) of new cases and 4 out of 5 (80%) of recurrent cases.

Eight out of the 12 patients underwent liver resection: 3 central hepatectomies, 1 left hepatectomy, 4

non-anatomical resections of the involved segments, and 4 enucleations. One of the patients in the liver resection group had tumor emboli in the left hepatic duct, which was removed during the surgery, and hepaticojejunostomy was done. Enucleation was done when the lesion was close to the hilum and major vessels and at difficult locations (segment 8, 4A, 2). All 4 patients in the enucleation group had an intraoperative frozen section of the cyst wall to rule out malignancy. The diagnosis of intrahepatic biliary cystadenoma was confirmed by histopathology in all patients. All the specimens were subjected to histopathological. The cuboidal lining of the cyst with subjacent cellular compact ovarian-like mesenchymal stroma was demonstrated in all cases. The diagnosis was confirmed with immunohistochemistry (IHC), showing nuclear positivity for estrogen receptor (ER) and progesterone receptor (PR). There was no evidence of malignancy in any of these patients.

Median cyst size was 11 cm (range: 7-39 cms). The largest lesion measured was 39x28 cms, which is the largest biliary cystadenoma reported to date to the best of our knowledge. (Table 2)

Intraoperative blood loss ranged from 150-950 mL (median 350 mL). Immediate complications in the postoperative period occurred in 3 patients in the form of bile leak, which gradually subsided over a period of 7-14 days. None of these patients required

Table 2: Details of surgical procedures.

S. No	Segments involved	Size (cm)	Recurrent cyst	Procedure	Complications
1	4B,5	7x9	No	Enucleation	Nil
2	4,5,8	15x10	Yes	CH	Bile leak
3	4,5,8	12x7	Yes	CH	SAIO
4	4B,5	15x8	No	Enucleation	Nil
5	4,5,8	10x8	Yes	CH	Nil
6	2,3,4A	14x6	No	LH	Nil
7	5,6	8x6	No	NAR	Bile leak
8	6,7	7x8	Yes	NAR	Nil
9	2,4A	9x7	No	NAR	Nil
10	4B,5,6	39x28	Yes	Enucleation	Bile leak
11	7,8	16x10	No	NAR	Cardiac arrest
12	5,6,7	8x12	No	Enucleation	Nil

*CH-Central hepatectomy, LH-Left hepatectomy, NAR-Non anatomic resection.

endoscopic, radiological, or surgical intervention. One patient had postoperative cardiac arrest possibly due to air embolism and developed post cardiopulmonary resuscitation hypoxic-ischemic encephalopathy. None of the patients developed surgical site infections. In the long term complication, 1 patient developed adhesive subacute intestinal obstruction 2 years after central hepatectomy and underwent laparotomy and adhesiolysis for the same.

All the patients were followed up in OPD with ultrasonography (USG) of the abdomen to rule out recurrence. Initial ultrasound was done at three months after surgery and then every 6 months. The longest follow up was for seven years post-surgery, and the shortest was three months. None of the patients had a recurrence of cyst during a median follow-up of 24 months.

Discussion

Biliary cystadenomas constitute less than 5% of cystic space-occupying lesions of the liver. It occurs typically in middle-aged women presenting with abdominal pain, discomfort, fullness, and sometimes a palpable mass. Asymptomatic cases have been reported when the size is small.^{1,6,7,14} Rare presentations include jaundice, vomiting, anorexia, and weight loss.^{14,15} It can present acutely with pain abdomen due to intracystic hemorrhage or rupture of the cyst and also fever due to secondary infection of the cyst.¹⁶ The near-exclusive occurrence in females and the associated increase in size during pregnancy and following oral contraceptives suggest hormonal dependence.^{1,2,13}

In the present case series, abdominal pain was the most common symptom followed by abdominal fullness and mass abdomen. One patient had obstructive jaundice. Biliary cystadenomas are usually multiloculated, septated cystic tumors, and comprise of two types: with and without ovarian-like stroma.^{1,5,8} Edmondson *et al.* initially defined BCAs in 1958 as multilocular lesions with ovarian-like stroma, but subsequently, BCAs without ovarian stroma were reported. The ovarian-like stroma consists of compact spindle-shaped cells and supports the epithelium and is often seen exclusively in women.^{1,7,16} Microscopically they have loculi, which are limited by a single layer of cuboidal or columnar epithelium resting on a basement membrane with multiple

polypoidal or papillary projections. Cystadenomas with ovarian stroma are considered pre-malignant with a good prognosis, while those without ovarian stroma have a higher risk of transformation to malignancy and have a poorer prognosis.^{6,8,9} The lesions with ovarian stroma closely resemble mucinous cystadenomas of the pancreas; hence biliary cystadenomas were recently redefined as a mucinous cystic neoplasm of liver (MCN-L) in the 2010 World Health Organisation (WHO) classification.³¹

The majority of biliary cystadenomas do not communicate with the bile ducts, but rarely it may be present.^{2,17} None of the patients in our case series had cysto-biliary communication. Intracystic fluid may be clear or mucinous.^{5,7} The presence of blood-stained intracystic fluid should raise the suspicion of cystadenocarcinoma. Rarely the fluid may be bile stained, purulent, or gelatinous.⁹ Differential diagnosis of cystadenomas includes simple liver cysts, parasitic cysts (particularly hydatid cyst), liver abscess, polycystic liver disease, biliary cystadenocarcinoma, and cystic metastases.^{9,10,14} In our series, 4 patients were misdiagnosed as hydatid cyst and 1 as simple cyst of liver and operated elsewhere.

Preoperative diagnosis of biliary cystadenomas poses a challenge for both radiologists and surgeons as the symptoms are non-specific, and imaging findings may be similar to other cystic lesions of the liver. A high index of suspicion is required for accurate diagnosis in the preoperative setting. With considerable experience, it is often possible to make a diagnosis on imaging in the form of ultrasonography, CECT, and MRI abdomen (**Figure 1,2**). On all these imaging modalities, the presence of a multiloculated cyst, septations, and internal echoes, with papillary projections is typical.^{9,15} CECT also

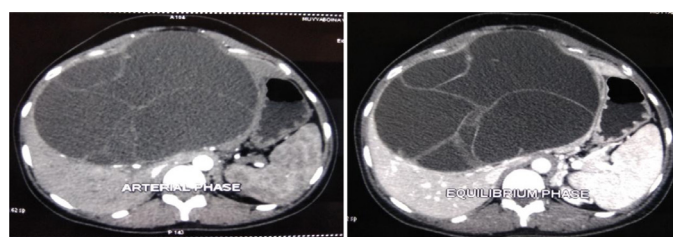


Figure 1: Triphasic CT(axial sections) showing multiloculated cyst in liver with enhancing septae and mural nodule (arrow).

delineates the anatomic relation to surrounding structures, particularly major vessels.^{14,15,18,19} MRI can characterize the nature of fluid within the cyst^{9,18}, that is blood or mucin. In spite of the advanced imaging modalities and aforementioned radiological features, the preoperative radiological diagnostic accuracy may be as low as 30% leading to misdiagnosis²⁰. Therefore a high index of suspicion is required in cases with a multiloculated, septate liver cyst, central location, recurrent cyst after previous partial resection. Although cross-sectional imaging can reliably differentiate cystadenomas from other cystic lesions of the liver, it may not be able to differentiate it from cystadenocarcinoma. An irregular thickness of the cyst wall, presence of mural nodules, or papillary projections are indicative of a malignancy.^{9,10,18,21} Hypervascularity of mural nodules on CT also suggests malignancy.²² Hence, the confirmation of the diagnosis is always by histopathological examination of the resected specimen. In our series, CT had shown multiple loculi and septations in all patients. Enhancing septae and mural nodules were seen in 6(50%) and 3(25%) patients, respectively. A preoperative core needle biopsy or FNAC to detect malignancy is not recommended, especially in operable lesions due to low accuracy and the risk of needle seeding and dissemination.^{16,23,24} Elevated CEA and CA 19-9 in the serum or cystic fluid may aid in the diagnosis and follow-up of patients.^{16,25} Pinto and Kaye, in their study, utilized intracystic CEA levels to differentiate BCA from benign cysts with 100% sensitivity and 94% specificity.²⁶ A normal level, however, does not exclude a biliary cystadenoma; hence these procedures are not commonly done. In our series, only 3(25%) out of 12 patients had a raised preoperative CA 19-9 levels. The role of cyst fluid CEA, CA19-9, and serum tumor markers remains controversial as the sensitivity and specificity are not high enough to differentiate a biliary cystadenoma from cystadenocarcinoma.

The important issues while diagnosing and treating a case of BCA are the incomplete excision of the cyst, misdiagnosis as a simple or a hydatid cyst, and the difficulty in differentiating cystadenocarcinomas, either pre or intraoperatively.^{1,5,9,12} Intraoperative frozen section of the cyst wall is a useful aid in such situations as it can differentiate a biliary cystadenoma from other

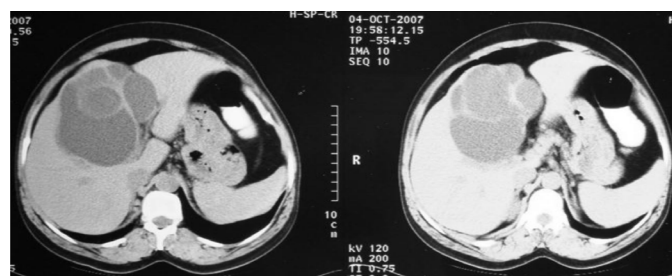


Figure 2: Recurrent biliary cystadenoma in segment 4,8 of liver.

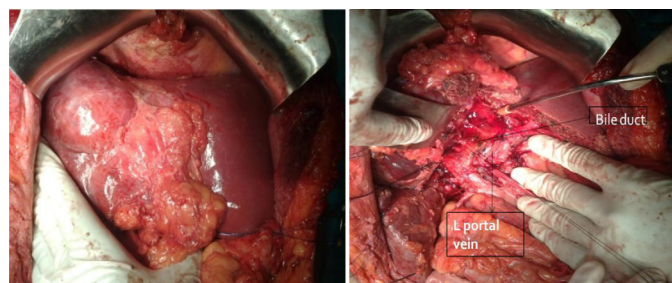


Figure 3: Recurrent biliary cystadenoma, remnant liver after central hepatectomy.

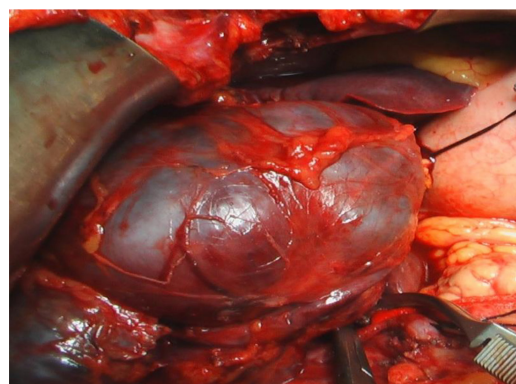


Figure 4: Biliary cystadenoma arising from segment 4B and 5 of liver.

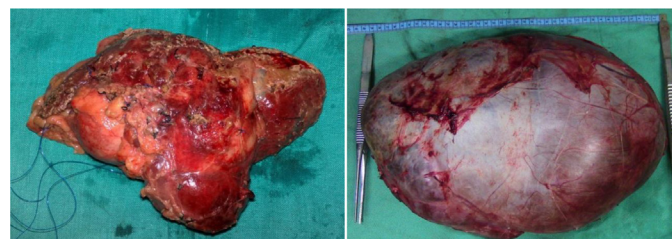


Figure 5: Specimens (a) Liver resection (b) Enucleation (39x 28 cm cyst).

cystic lesions of liver but not biliary cystadenocarcinoma. Historically, BCA's have been treated with procedures like deroofting, Roux-en-Y cystoenterostomies, aspiration, or partial resection. However, these procedures have been associated with a high risk of recurrence^{7,9,14,27,28}. Hence, complete resection is the recommended treatment with negligible recurrence^{1,5,8,12} (**Figure 3**). Pinson *et al.* have reported cyst enucleation without late recurrence and mortality.²⁹ This procedure is a valid alternative where resection is difficult or is likely to be associated with higher morbidity.^{12,16}

Laparoscopic resections of biliary cystadenomas have been described with similar morbidity and recurrence rates as open resection, the largest series being reported by Koffron *et al.* [30], who reported only 1 recurrence out of 22 patients who underwent a laparoscopic procedure for biliary cystadenoma. Whether the approach is open or laparoscopic, the aim should be complete resection of the lesion.

In conclusion, the diagnosis of biliary cystadenoma should be considered in any multilocular cystic lesion of the liver, especially recurrent cysts, particularly in a middle-aged woman. It is most commonly misdiagnosed for a hydatid cyst, especially in endemic regions, as seen in our series. Hence it should form the part of differential diagnosis of multiloculated cystic lesions of the liver. Complete resection of the cyst is recommended when in doubt. The recommended treatment of choice for any suspected BCA is resection, as it is challenging to differentiate it from cystadenocarcinoma preoperatively. Enucleation is another feasible option and is indicated where resection is difficult due to the location of the tumor or proximity to the hepatic hilum and major vessels. (**Figure 5**)

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