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Review Article

Biliary Cystadenoma – A Literature Review

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Abstract

Biliary cystadenoma (BCA) is a pre-malignant, unilocular or multilocular cystic disease of liver, presenting commonly in middle-aged women with the mean age of 50 (range 38 – 64) years. It accounts for 5% of all cystic disease of liver. Differential diagnosis varies from simple liver cysts to cystic liver metastases. Aetiology of this lesion is unclear, but congenital and acquired theories have been proposed. It has variable size with smooth surface and internal septations. Some BCAs presents with nodules and/or papillary excrescence. Ovarian stroma is a striking feature, but BCAs without ovarian stroma have been reported. Clinical symptoms vary from vague abdominal pain to obstructive jaundice. Obstructive jaundice may be due to external compression or luminal communication with mucobilia. Some patients present with acute abdominal pain due to infection or intracystic haemorrhage. Radiological imaging has low accuracy in diagnosing BCAs. Ultrasound, CT, MRI, MRCP, ERCP, intraoperative cholangiogram and choledochoscopy have been described in the literature for the diagnosis of BCA. Preoperative cyst fluid aspiration and FNA are generally not recommended. Due to its pre-malignant nature and tendency to recur, formal surgical resection with negative margin is recommended. Cyst enucleation is an alternative, where surgical resection is not possible.

Keywords: Biliary Cystadenoma; Biliary Cystadenocarcinoma

Abbreviations

BCA: Biliary Cystadenoma;

IPNB: Intraductal Papillary Neoplasm of Bile Duct;

CEA: Carcino Embryonic Antigen;

WHO: World Health Organisation;

FNA: Fine Needle Aspiration

Introduction

Biliary cystadenoma (BCA) is a rare, benign, premalignant unilocular or multi-locular cystic lesion of the biliary system occurring most commonly in women [1-5]. It commonly arises from the intrahepatic bile duct and 10-20% of BCAs of extra hepatic biliary tract and gall bladder have been reported [2,6-10]. It accounts approximately 5% of all hepatic cystic lesions [11].

BCA was reported first in the literature 1887 and the surgical treatment for BCA was first performed in 1892 [12]. Developments in modern imaging and safe liver surgery lead to increase in the number of reported cases in the literature in 1990s [13,14]. Differential diagnosis of BCA includes, simple cysts, parasitic cysts (especially hydatid cyst), haematomas, post-traumatic cyst, liver abscess, polycystic liver disease, biliary cystadenocarcinoma, metastatic ovarian or pancreatic adenocarcinoma [2,4,15]. Choledochal cyst is an important differential diagnosis for extra-hepatic BCAs [16].

The incidence of BCA is between one in 20,000 to 100,000 people, while the occurrence of cystadenocarcinoma is approximately one in 10 million patients [17]. Even though the previously published literature quoted the incidence of BCAs to be around 5% of cystic hepatic tumours, still it is unclear about the true incidence [13,18,19]. The controversy is due to lack of established criteria for preoperative diagnosis of unilocular BCAs [7,13,20,21]. Due to its premalignant nature and tendency to recur, treating this tumour with techniques other than formal resection causes great concern [3-5,19,22-24].

Aetiology

Aetiology of BCA is unknown [11,25]and both congenital and acquired origins have been proposed. Presence of hamartomatous structures supports the theory of congenital origin [26]. Cruickshank et al proposed a theory of acquired lesion and development of BCAs as a reactive process to focal injury has been reported [3,27]. It was also suggested that this might have arisen from ectopic embryonal tissue destined to form gall bladder or from ectopic embryonic rest of primitive foregut sequestered with in the liver [3,19,28,29]. Presence of endocrine cells in BCAs and cystadenocarcinomas also suggest the origin from peri-biliary glands [30].

The development of cystadenocarcinomas is unclear. However, it is generally believed that they arise from BCAs as many cystadenocarcinomas contain areas of BCAs in the same sample [3,19,21,23].

Pathology

BCAs often have a globular shape with varying sizes from 1.5 to 35cms. They have smooth external surface with underlying multi-locular cyst filled with mucinous fluid and divided by irregular thick walls [3,18,24,32,33]. Luminal communication with the bile duct may be occasionally found with BCAs [18,34]. In some occasions the dysplastic mucinous epithelium develops inside the bile duct, which causes biliary obstruction [35]. These lesions are considered as IPNB with cystic dilatation rather than true biliary cystic lesions [34,36].

BCAs are composed of communicating, variable sized locules usually containing clear fluid. The locules are lined by simple, predominantly columnar epithelium resembling biliary epithelium with cytoplasmic mucin [25]. The epithelium may show denuded areas with chronic inflammation and haemorrhage and some cysts exhibit focal severe dysplasia and diffuse intestinal metaplasia – including goblet cells, Paneth cells, and endocrine cells – within a mucinous-type epithelium arranged in prominent papillary excrescences [37] . The majority of lesions have shown mesenchyme (ovarian) stroma (MS) which has shown immune reaction to estrogen and progesterone receptors on immuno- histochemistry. The epithelial cells have been reported showing strong reaction with carcino embryonic antigen (CEA) immunostain and focally reactive with CA125, with intensities varying from mild to strong. The MS cells showed moderate to strong immunoreactivity to oestrogen receptors (ERs) and mild to strong positivity to progesterone receptor (PR) immunostain. The MS cells showed no immune reaction with CEA and CA125 stains for any patients [37].

Edmondson initially defined BCAs in 1958 as multi-locular lesions with ovarian like stroma, but subsequently BCAs without ovarian stroma were reported [5]. BCAs with ovarian stroma have good prognosis even though they are premalignant, but those without are considered to have high risk of malignant transformation with poor prognosis [5,15,38,39]. The WHO which initially classified BCAs as biliary cystadenoma/adenocarcinoma in 2000, redefined these lesions in 2010 as either mucinous cystic neoplasm (MCN) or intraductal papillary neoplasm of bile duct (IPN-B) depending on the presence of ovarian stroma and growth with in the bile duct, respectively [40,41].

The epithelium may show varying degrees of dysplasia. High grade dysplasia or invasive carcinoma suggests transformation to cystadenocarcinoma [25]. Devaney et al proposed three subsets of cystadenocarcinoma based on the pathology material submitted to their institutional laboratories for primary diagnosis or consultation: [1] cystadenocarcinoma originating from a benign cystadenoma with ovarian-like stroma, occurs exclusively in women; [2] de novo cystadenocarcinoma occurring almost only in men; and [3] cystadenocarcinoma that occurs in women but does not contain an ovarian-like stroma [5].

Clinical features

Common presentations of BCAs include, vague abdominal discomfort, nausea, anorexia and some times with palpable mass [3,9,19,22,4]. These vague abdominal complaints may be secondary to extrinsic compression of stomach, duodenum or biliary tree [5,19,42]. Ascites may develop secondary to compression of hepatic veins or vena cava [11]. Thomas et al reported in his series with abdominal pain in 74%, abdominal disten-

sion in 26%, and nausea/vomiting in 11% of the patients [20]. BCAs have known to increase during pregnancy and with oral contraceptive pills, exhibit its hormonal dependency nature [13,18,19]. Liver functions tests are usually normal [22,24].

Acute presentations include obstructive jaundice [5,19,42], rupture, bacterial infection, intracystic haemorrhage [21,43]. Obstructive jaundice may be due to external compression or mucobilia [19,24,44]. A rare case of BCA presenting with pleural effusion has been reported in the literature [45]. But BCAs has also been identified in asymptomatic patients during imaging or surgical exploration for unrelated clinical conditions [46].

Preoperative Investigations

Even with improved imaging techniques, it is still challenging to differentiate BCAs from other cystic lesions of the liver. Differential diagnosis for BCAs includes simple liver cysts, parasitic cysts, haematomas or post-traumatic cysts, liver abscesses, congenital cysts, polycystic disease, Caroli's disease, and neoplastic lesions such as biliary cystadenocarcinoma, undifferentiated embryonal sarcoma, cystic metastasis, metastatic pancreatic or ovarian cystadenocarcinoma, biliary papilloma, cystic primary hepatocellular carcinoma, cystic cholangiocarcinoma, and hepatobiliary mesenchymal tumours [2,47,48].

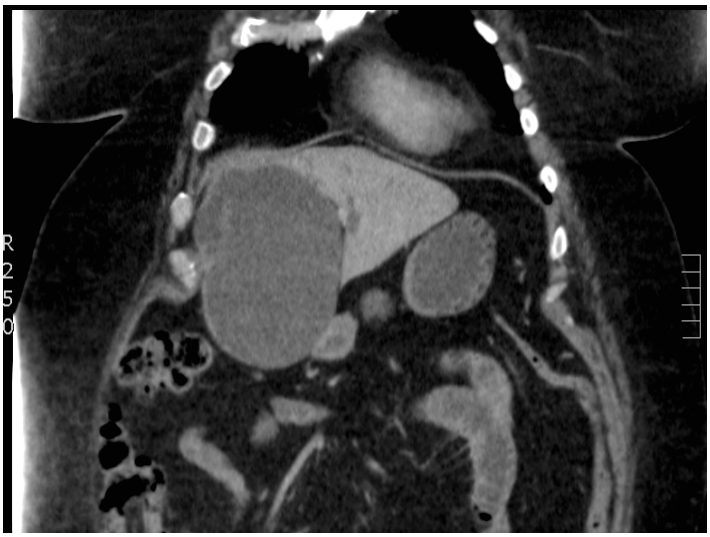

Figure1. CT scan showing biliary cystadenoma without septation.

Ultrasound scan, CT (Figure 1), MRI (Figure 2) of the liver, MRCP, ERCP, intraoperative cholangiography and choledochoscopy all have been described in the literature for the pre-operative work up of BCA [49-53]. Although radiologic features such as papillary projections, internal septations, wall thickness, irregularities, calcification and mural nodules suggest the possibility of a BCA, all of these except papillary projections may be observed in simple cysts as well albeit at a lower frequency [54-56]. Classical findings on ultrasound are an anechogenic mass with internal septations that are highly echogenic. Computed tomography classically shows a smooth thick-walled cyst with fine internal septae [49,57]. MRI is a valuable tool for the diagnosis and differentiation of cystadenoma from other cystic liver lesions while combination of MRI with MRCP is even more useful for this purpose [51]. On T1-weighted images, MRI reveals a fluid-containing, multi-locular, septated mass with homogenous low signal intensity, the wall and septa of which become enhanced after administration of Gd-DTPA [2,51,58]. Doppler study may show the vascular flow within the lesion [54,59]. Hypervascularity of mural nodules and irregular wall thickness on CT also suggests malignancy [2,5,49,60]. CT and MRI usually fail to show the biliary communication with the BCAs, but intraoperative cholangiogram demonstrates this communication accurately [18,34]. Preoperative radiological diagnostic accuracy may be as low as 30%, so high index of suspicion is indicated in diagnosis of BCA [61].

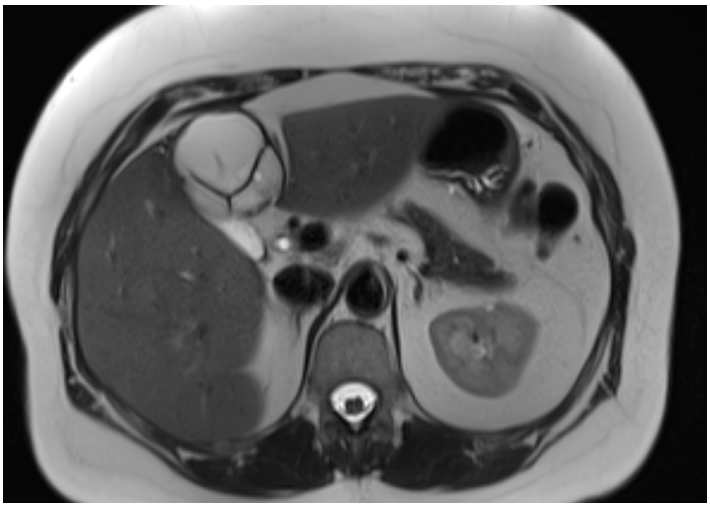

Figure 2. MRI pictures showing BCA with septations and nodule.

Elevated levels of serum CA 19-9 and carcinoembryonic antigen (CEA) have been reported; however, this is a variable finding [62]. Preoperative cyst fluid aspiration for diagnosis has been advocated in the published literature. Cyst fluid CA19-9 and CEA levels can be helpful to enhance the accuracy of diagnosis of BCAs and cysadenocarcinomas from other cystic lesions [11,17,63]. A normal level does not exclude a biliary cystadenoma; some simple liver cysts may also show elevated serum or cystic fluid CEA or CA 19-9 [17]. Percutaneous fine needle aspiration also provides fluid for bilirubin concentration analysis, which is suggestive of communication of cystadenoma with the biliary tract when it is elevated [17].

Preoperative FNA is not accurate in differentiating BCAs from cystadenocarcinoma, as inadequate sampling may miss the microscopic foci of carcinoma in the cystadenoma [37,63,64]. Preoperative differentiation of BCAs from cystadenocarcino-

ma is extremely difficult and can only be done after pathological examination [1,3,19,29,46,48]. FNA and needle biopsy may risk dissemination of tumour cells and it is not generally recommended, especially when surgery is planned [11,64]. EUS guided aspiration and FNA of cystic lesions were suggested as an alternative to percutaneous approach, but the above issue still not resolves with EUS guided FNA [65]. Improper preoperative diagnosis can lead to incorrect and unnecessary procedures such as percutaneous aspiration, ethanol injection, de-roofing, omentoplasty etc [38].

Table 1. Prognosis in various liver malignancies.

Pathology	Disease status	5 year Survival	Recurrence rate
Cystadenocarcinoma [44]	Surgical resection with positive margin	65 – 71%	13%
	Surgical resection with negative margin	100%	
Hepatocellular carcinoma (SEER data 2003 – 2009)	Localised	28%	
	Regional	7%	
	Distant metasteses	2%	
	After surgical resection [73]	50%	70 – 100%
	After liver transplant [74]	60- 70%	15 – 20%
Intrahepatic cholangiocarcinoma (SEER data 2000 – 2006)	Localised	15%	
	Regional	6%	
	Distant metastases	2%	
	After surgical resection [75]	50%	46%
Colorectal Liver metastases	After surgical resection [76]	45 – 60%	60 – 85%
	Un resectable [77]	0%	

Treatment

Due to its premalignant nature and lack of reliability of imaging and preoperative aspiration cytology in differentiating BCA from cystadenocarcinoma, all lesions suspected of BCA should be surgically removed with negative margin [17,18,20,38,66-68]**.** Patients with large BCAs and lesions confined to few segments should be treated with formal hepatectomy [38]. If BCA is suspected on imaging, surgery is indicated even if the patient is asymptomatic [1,19,29,46,58,64]. The extent of resection remains to be determined, as partial resection with occasional ablation of the residual cyst using electrocautery or argon beam coagulation and/ or omentopexy, lobectomy, wedge resection and enucleation have all been reported [14,17,21,29,30,69,70].

Other limited procedures like aspiration, fenestration, internal drainage, sclerotherapy and partial resection are associated with extremely high recurrence ranging from 90 -100%, compared to 0-10% with formal resection [4,20,21,32,38,42,64,69 ,71,72]. Pinson et al. have reported cyst enucleation without late recurrence and mortality [14]. This procedure is a valid alternative where resection is difficult or is likely to be associated with morbidity [11,20].

Prognosis

The prognosis of patients with BCA is good if total excision of the lesion is performed [3,5,19,20,64]. Even biliary cystadenocarcinoma has good prognosis compare to other hepatic malignancies, as they exhibit less aggressive clinical behaviour with slow growth and less frequent metastases [38,64] (Table 1).

Conclusion

Possibility of BCA should be considered when a multi-ocular lesion is found in middle-aged women. When suspected surgical resection is the most successful therapeutic option and procedure of choice, as it is extremely difficult to differentiate this from biliary cystadenocarcinoma. Surgical enucleation is an alternate option where resection is not possible. BCAs can be resected safely with significantly low morbidity. Complete surgical resection provides a cure.

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