Case Series

Intra hepatic biliary mucinous cyst adenoma (BMCA): varied presentation and management options

Mimi T Ganguly[1], Ritankar Sengupta[2], P. Sivakumar[3], Rinki Das[4]

[1]Associate Professor, Department of Pathology, North Bengal Medical College, Darjeeling,West Bengal, India
[2]Assistant Professor, Department of General Surgery, NRS Medical College, Kolkata, West Bengal, India
[3]Postgraduate Trainee, Department of General Surgery, IPGME&R- SSKM Hospital, Kolkata, West Bengal, India
[4]Associate Professor, Department of General Surgery, IPGME&R- SSKM Hospital, Kolkata, West Bengal, India

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Abstract

Benign cystic neoplasms of liver comprises of 5-10% of hepatic lesions. While simple cysts are common, biliary mucinous cystic tumors (BMCT) are rare tumors. We report various presentations of benign mucinous cystadenoma (BMCA), ranging from a small well defined cystic lesion to large lesions replacing one lobe of liver or involving multiple sectors of the liver, requiring a wide range of surgical procedures to treat such tumors. Histopathology confirmed the diagnosis of benign biliary cystic neoplasm in all the cases. Rare occurrence, potentially malignant nature of the disease and difficulty in differentiating from other cystic hepatic lesions need careful evaluation of such cases to select the optimum management option.

Keywords: Intrahepatic biliary mucinous cystic neoplasm, biliary mucinous cystadenocarcinoma, cystic hepatic tumor, biliary cystadenoma.

Introduction

Case 1

43 yrs old lady presented with gradually progressing abdominal heaviness, early satiety with reduced food intake and an abdominal mass for 10 months. Abdominal examination revealed hepatomegaly with a smooth surface. Sonography revealed a 15 x 13.8 x 10.2 cm cystic lesion occupying the segment IV, segment V and VIII of liver compressing on the hilar structures. There was no daughter cyst. ELISA for Echinococcal IgG was negative. CECT abdomen demonstrated a large encapsulated homogeneous cystic lesion with few septations without any solid component. The cyst was displacing the bifurcation of the portal vein and common bile duct distally, and the posterior wall of the cyst was lying on the IVC.

In view of central location of the cyst complete excision was not possible, but persistent pressure symptoms prompted us to plan for a laparoscopic partial cystectomy. On diagnostic laparoscopy, a centrally located huge cyst was found which showed clear fluid on aspiration. Marsupialisation of the cyst was contemplated, but facing difficulties in hemostasis the procedure was completed with a small midline incision. Cyst wall sent for histopathological examination revealed a benign biliary cystadenoma. The patient recovered well and remained free from symptoms. After a year, a repeat CECT abdomen revealed the remaining cyst approx 8 cm in diameter in the same location. The patient was followed up for 5 years and reported mild symptoms of upper abdominal discomfort which was managed conservatively.

**Correspondence*
Rinki Das
Associate Professor, Department of General Surgery, IPGME&R-SSKM Hospital, Kolkata, India
E-mail: rinkid123@gmail.com

Case 2

A 47 yrs old woman presented with upper abdominal heaviness and a gradually enlarging abdominal mass for one year. There were no associated gastro-intestinal or constitutionalsymptoms. Abdominal examination revealed a smooth & variegated hepatomegaly. Earlier, she was diagnosed to have an incidental cystic hepatic mass on sonography and had undergone laparoscopic aspiration in 2009. She remained asymptomatic since then.

Abdominal sonography revealed a 20 cm cystic lesion in the left lobe of liver. It had heterogeneous exophytic component containing multiple smaller cysts. Left adnexa had an incidental 4 cm dermoid cyst. Contrast enhanced CT scan of the abdomen revealed a large solid-cystic lesion involving the left lobe of liver and the segment VIII measuring 20 x 14x 19 cm; multiple fine internal septations were suggestive of a biliary cystadenoma. The exogenous component caused mass effect on the stomach, duodenum and pancreas. Main portal vein, its right branch and right hepatic vein were normal. Left portal vein, middle and left hepatic veins were not visualized. Liver volume was1140 ml. CT scan also confirmed presence of the left adenexal dermoid. Contrast enhanced MRI showed cystic components with T1 hypointense and T2 hypertintense signal intensity and multiple thin septations. There was a heterogenous soft tissue mural nodule of 8.2 x 7 x 6 cm with T1 hypointensity and T2 hyperintensity. It showed heterogenous enhancement on post contrast images and restriction on DWI. These findings were suggestive of a mucinous cystic lesion of the liver. No cysto-biliary communication was identified. Hydatid serology was negative and CA-19-9 was 7.99 IU.

On exploration, a large 15 x 10 x 20 cm cyst was present in the left lobe of the liver. Due to massive size of the lesion and difficulty in mobilization, it was felt necessary to decompress it. 2.5 liters thick bilious fluid was evacuated from the cyst. Intra operative cytology

from mural nodule showed no evidence of malignancy. Excision of left lobe harboring cyst along with nonanatomic resection of segment VIII was performed. No obious cysto-biliary communication was identified during surgery.

Cut open cyst revealed a solid mural nodule and multiple cystic components with smooth inner lining of the giant cyst [Fig. 1]. There was no papillary projection inside the cyst. No cysto-biliary communication was identified. The resected cyst was stained with haematoxylin and eosin. It revealed mucinous glands lined by low columnar epithelium, with low grade dysplasia, without any papillary projection inside the lumen. The inner epithelium was surrounded by ovarian like stroma, which was strongly positive for estrogen and progesterone receptors. The excised left adenexal cyst was consistent with dermoid cyst.

At three year follow up, the patient is doing well without any recurrence.

Case 3

A 48 yr old lady presented with heaviness in the upper abdomen for 2 years. Labs demonstrated a total bilirubin level of 1.8 mg% and alkaline phosphatase level of 463 IU. Other liver enzyme levels were within normal range. CECT abdomen demonstrated a 8cm x 6 cm x 5.5.cm thin walled cystic lesion in segment 3 of the liver with multiple septations without any solid component. Serology for echinococcusgranulosus was negative. Fine needle aspiration cytology revealed clear fluid. No parasite or malignant cell was detected. In view of persistent symptoms and mildly elevated serum alkaline phosphatase level resection of the hepatic cyst was carried out. On exploration a cystic lesion was revealed in segment 3 of the liver abutting the hilum. Non anatomical resection of the cyst was carried out. Cut surface revealed a 8.5 cm x 6 cm mutiloculated lesion lined with bile stained epithelium. Histopathology examination revealed a thin walled cyst lined by columnar epithelium beneath which there was stromal tissue resembling ovarian stroma. Cytological atypia or architectural complexity was not seen [Fig.2].

At one year follow up the patient is doing well without any recurrence.

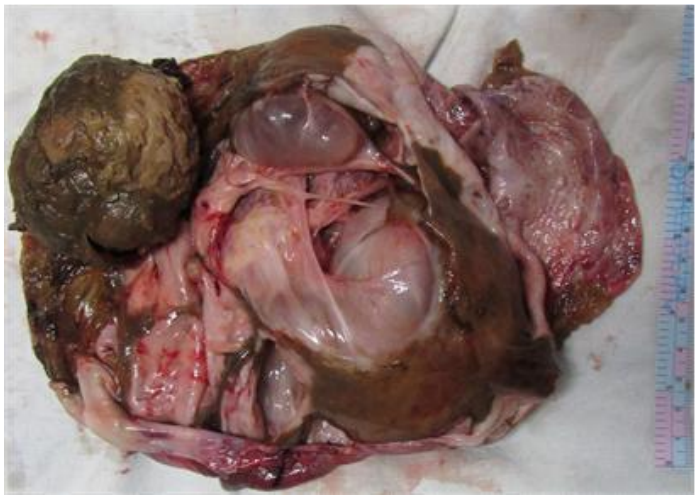

Fig. 1: Cut open cyst showing intracystic solid mural nodule (white arrow) and adjacent bile stained cyst wall (Case 2)

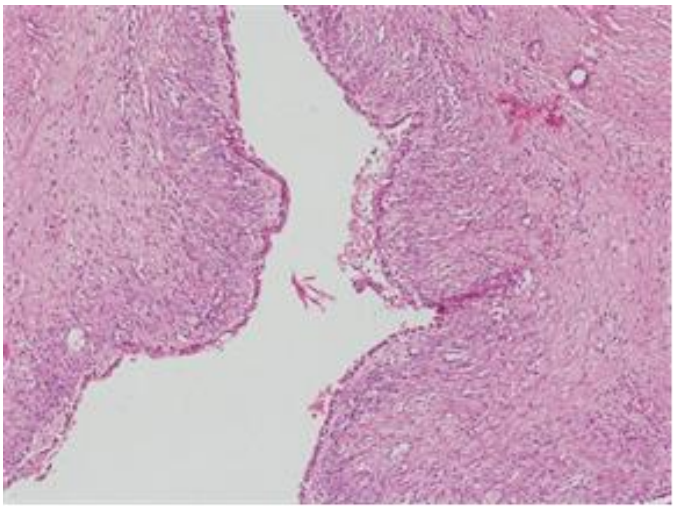

Fig. 2: H-E stained specimen showing mucinous glands lined by low columnar epithelium and ovarian stroma

Discussion

Primary intrahepatic BMCA occurs most commonly in females in their fifth decade of life. Wang et al.[1] in their series of 14 patients

with biliary cystadenoma also reported the female preponderance (78.6%). All our cases were middle aged ladies. It is mutilocular in up to 84% of patients and the size varies from 1cm-40 cm. The tumor shows predilection for left lobe of the liver [2, 3] as we have also observed in our cases, two cases were found to be taking origin from the left lobe of the liver, and another one was occupying the central location. The etiology of BMCT remains idiopathic. It is hypothesized to arise from ectopic ovarian cells migrated into the liver during embryonic development in female[4]. The right and left primordial gonads are located directly under the diaphragm prior to their descent in the pelvis. This theory also explains frequent occurrence of BMCNs in segment IV of the liver in the paramedian location. These tumors typically do not communicate with the bile duct. However, in 3-4 % cases there may be biliary communications [4]. Half of BCTs contain endocrine cells suggesting that they may originate from intrahepatic peri biliary glands[5].

BMCA patients are generally asymptomatic, but may complain of right upper quadrant pain, discomfort, or awareness of an abdominal lump. Less frequent complaints include fever, weight loss, jaundice, and ascites [2, 3, 5]. Compression of portal vein and IVC has also been reported and such presentation may hinder their complete excision, as we have observed in one of our cases also. Tumor rupture, intra-abdominal hemorrhage, and fever from secondary infection are infrequent presentations[6]. Recurrent jaundice with cholangitis has also been reported although very rare; and may be attributed to extraluminal compression of the bile duct or intra-ductal tumor extension without malignant invasion or viscid intraductal mucin emboli[7].

Classically, BMCA is characterized by ovarian-type stroma that typically expresses estrogen and progesterone receptors (60-100%) [8]. This may explain its high incidence among females[8], increase in size during pregnancy and in patients on hormonal therapy[9]. In all the cases of our series, the cyst had strong positivity for estrogen and progesterone receptors. However, defining BMCA based solely on the presence of ovarian stroma may be insufficient since a number of these tumors lack this stromal component[6].

BMCC may arise from a BMCA with ovarian-like stroma or it may arise*de novo* from bile ducts. The presence of mesenchymal (ovarian-like) stroma has important prognostic implications. Since BMCC without mesenchymal stroma, disseminates more rapidly, and is associated with a worse prognosis than BMCC with ovarian stroma[10].

The World Health Organization (WHO) in 2010 had re categorized biliary cystadenoma into mucinous cystic neoplasms with low-, intermediate, or high-grade intraepithelialneoplasia and biliary cystadenocarcinoma into mucinous cystic neoplasms with an associated invasive carcinoma[11].

With advances in imaging techniques, more and more such tumors are being detected now-a-days. The appearance on imaging is that of a complex liver cyst. Sonographically, biliary cystic tumors (BCTs) are anechoic, have thickened irregular walls and internal septations[12-13]. Septal thickening, papillary infolding, and mural nodules are characteristic of BCTs. With the use of injectable contrast enhancement of the cystic wall, internal septation, and intra-cystic solid component in the arterial phase are observed. The enhancement generally gets washed out progressively and appears as hypo-enhancement in the portal and late phases. These features differentiate a Bilary Mucinous Cyst Adenoma (BMCA) from a simple hepatic cyst however, distinguishing between cystadenoma from cystadenocarcinoma remains difficult because these lesions have similar imaging characteristics. A large (>1 cm) mural nodule or gross infiltration to the surrounding liver or bile duct is suggestive of a malignant cyst[12].The index case had characteristic CECT imaging of big cystic lesion in left lobe, presence of multiple septa, heterogenous appearance along with mural nodule. This imaging was suspicious of malignancy. Hence, we performed intra operative cytology to rule out malignancy.

CT and ultrasound are complementary modalities in evaluating BCT. Sonography is moreuseful at detecting septa in cystic lesions whereas CT more accurately reveals the anatomic extent and size of the lesion [14].

MRI is another useful tool in evaluating BCT. BCT are typically multi-locular with irregular thick walls on MRI[15]. Cyst fluid typically gives low intensity T1 signal and high intensity T2 signal[16]. Linear low signal intensity within high intensity cysts identifies septations on T2 weighted images[16]. MRI also demonstrates the anatomic relationships within the liver and is useful for surgical planning. Diffusion weighted MR sequences improves cyst

characterization and detection of malignancy[17]. MRCP can also be helpful in demonstrating cystobiliary communication and internal septations[18].

Lately, PET-CT scan has been used to differentiate BMCC from BMCA. The malignant transformation increases FDG uptake by invasive BMCC[19]. There are no large series available in literature on the use of this imaging modality because of infrequent occurance of the disease and the limited availability of this investigation.

The differential diagnoses of such tumours would include simple liver cyst, hemorrhagic cyst, echinococcal cyst, liver abscess, atypical hemangioma, lymphangioma, hamartoma, undifferentiated sarcoma, intraductal papillary mucinous tumor, and primary or secondary necrotic neoplasms[20]. Differentiation from other benign lesions is important for the appropriate management of such tumor.

Simple liver cysts are well circumscribed echo-free lesions with indiscernible walls. On CT they appear as thin and smooth walled cysts with homogenous fluid attenuation. Rarely calcifications may be seen. On MRI simple cysts are hypointense on T1-weighted images and hyperintense on T2-weighted images[21]. Hemorrhage or infection of such a cyst may mimic a complex liver cyst. Ultrasound may show hyperechoic fluid with septations or solid components inside the cyst. CT shows hyperdense or heterogenous fluid and MRI shows high signal intensity on T1 and T2- weighted images[22]. MRI study in our series of patients proved to be beneficial in demonstrating the detailed features of the cysts.

Hydatid cyst is characterized by a primary intrahepatic cyst- a laminar structured wall surrounding fluid with multiple daughter cysts on ultrasound and computed tomography imaging. On magnetic resonance images free floating protoscolices and scolices are hypointense on T1-weighted images and distinctly hyperintense on T2-weighted images[23]. Moreover, infected patients usually show IgG and IgE antibodies to the organism[23]. All our patients were tested negative for hydatid serology.

Liver abscess appears as hypoechoic lesion poorly defined thick irregular walls with diffuse echogenic debris inside. On CT double-target sign of an enhancing circle surrounded by a hypoattenuating zone indicating parenchymal edema is frequently observed. Intra lesional gas may be present up to 50% cases and is an important distinguishing feature of an abscess. MR reveals a thick walled lesion with enhancement in delayed phases[24].

Cystic mesenchymal hamartoma is an uncommon liver lesion usually present in the first decade of life as a rapidly enlarging upper abdominal mass and is very rarely seen in adults[25]. On ultrasound this may appear as cystic or solid-cystic lesion with internal debris and a fluid-fluid level. There may be multiple thin septae inside the lesion. CECT shows enhancing intervening septae and T2 weighted MR shows high intensity fluid with intermediate high intensity thin septae[26]. FNAC is diagnostic and it shows both epithelial cells and mesenchymal spindle shaped cells and loose connective tissue[26].

Cystic giant hemangioma with large hypoechoic central areas may mimick a giant cystadenoma[29]. However, CT and MR show an enhancing rim with globular vessels and centripetal filling sparing the large central lacunar areas[27].

Hepatocellular carcinoma and mass-forming cholangiocarcinoma may present as large hypodense and multiseptated mass on

ultrasound mimicking a biliary cystic tumor. However, on CT arterial phase enhancement and wash out in the portal phase are diagnostic[28].

Isolated mucin producing metastases from melanoma or adenocarcinoma of colon may confound the diagnosis of a biliary cystadenoma. However, these lesions may be associated with segmental dilatation of the peripheral bile ducts[28].

Tumor markers have a limited role in the diagnostic work up for a complex cystic lesion in the liver. Elevated CA 19-9 serum levels could be helpful in differentiating simple hepatic cysts and BMCN[29]. However, some studies have demonstrated the dramatically increased levels of Ca 19-9 even in simple hepatic cysts as well[2,6]. CEA and CA 19-9 are normally secreted from the biliary epithelium and thus are not very specific for biliary mucinous cystic neoplasms. Tumour-associated glycoprotein (TAG) 72 (also known as CA72-4) is a glycoprotein present only on mucin antigens. It has been reported to be a promising marker to differentiate simple cyst from biliary mucinous tumors. Fuks et al[29] studied 118 patients of simple cyst and biliary mucinous cystic tumors and concluded that a TAG-72 concentration of more than 25 units/ml differentiated hepatic simple cysts from mucinous cysts.

Incomplete excision of primary intra hepatic BMCNs leads to recurrence, thus the mainstay of treatment is complete surgical resection of these tumours to prevent a recurrence[1,30]. Tumors extending in the major bile ducts may require excision of the bile duct with cholangio-jejunal anastomosis. Cysto-biliary fistulization without any invasion may be tackled by simple ligation or suture closure of the communication.

Aspiration, marsupialisation or partial excision of the cyst are associated with very high recurrence rates[1,3] even in benign tumors and are not recommended. Laparoscopic resection of BMCN has been found to be effective with conversion rate from 0-8%[20].

Frozen section from the cyst wall has been consistently proven effective in diagnosing biliary mucinous neoplasms, [31] although it may not correctly diagnose invasive disease.

Tumors occurring in females and containing ovarian-like stroma usually have a good prognosis while tumors occuring in elderly male patients and tumors with lymphatic invasion are associated with bad prognosis. According to growth types biliary mucinous cystadenocarcinoma may be divided into invasive type of biliary cystadenocarcinomas (carcinoma cells extending into the hepatic parenchyma or neighboring organs), which conceivably has a bad prognosis[32] while noninvasive type (carcinoma cells confined to the cystic lesions) have excellent prognosis. The prognosis of invasive BMCN is better than that of primary liver tumors if the lesion is completely resected, denoting its inherent less invasive potential. The overall 5-year survival after resection is 65-71% and can reach 100% if histologically negative resection margin is achieved[14]. In the series of twenty one patients by Lee et al[30], nineteen patients had intrahepatic biliary cystadenomas and two had biliary cystadenocarcinomas. Enucleation or hepatic resection was performed as a mode of treatment. Radical resection provided a significantly better clinical outcome in terms of tumor recurrence.

Conclusion

Large septated cystic or complex cystic lesion in left lobe of liver in middle aged females should raise suspicion of BMCT. CECT or MRI is standard imaging modality to differentiate from other complex cystic hepatic lesions. Presence of mural nodules or surrounding infiltration should alert clinician for presence of malignancy. Intraoperative cytology and or frozen section may differentiate BMCA from BMCC. Complete excision of the tumor which may range from non-anatomical resection to major hepatetomy as performed in two of our cases, is the treatment of choice to prevent recurrence. Larger symptomatic cysts not amenable for complete excision by major hepatic resections may require liver transplantation.

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