ANNALS OF GASTROENTEROLOGY 2009, 22(4):278-283

Case Report

Biliary Cystadenoma of the Liver: Case report and systematic review of the literature

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SUMMARY

Biliary cystadenoma is a very rare cystic neoplasm of the liver that usually occurs in middle-aged women. This tumour is insidiously progressive; it can not be safely differentiated from cystadenocarcinomas before operation and should always be considered for resection. The exact etiology of these tumors is unknown, but several theories have been proposed. Historically these cystic tumors have been treated by a variety of techniques including aspiration, fenestration, internal drainage, partial resection. Previously reported series have confirmed a greater than 90% recurrence rate with anything less than complete excision. In addition biliary cystadenoma is a premalignant lesion and only surgical excision can differentiate it from its malignant counterpart, biliary cystadenocarcinoma. A case of benign biliary cystadenoma with mesenchymal stroma is presented. This tumor was associated with elevated carbohydrate antigen 19-9 (CA19-9) which returned to normal 10 days after surgical enucleation.

Key Words: Biliary cystadenoma, cystadenoma, benign liver tumors, CA 19-9, mesenchymal stroma

INTRODUCTION

Cystadenomas of the liver are rare tumors that are infrequently reported. They account for less than 5% of solitary non parasitic cysts of the liver[1] and they occur in middle-aged women.[2,3] It is important to differentiate this neoplasm from other common hepatic cystic lesions such as simple cysts, abscesses, hydatid cysts and metastases which have different therapeutic management.

Biliary cystadenoma is considered a benign lesion with malignant potential (biliary cystadenocarcinoma)[3-5] and since it can not be safely differentiated from cystadenocarcinoma before operation they should always be considered for resection.[1-3, 6-8]

We describe here a case of benign biliary cystadenoma with mesenchymal stroma in which the cause of seeking medical advice was the accidentally found increase in the serum level of CA 19-9.

CASE REPORT

A 52 year old woman complained of vague upper abdominal pain. No other signs or symptoms were discovered on clinical examination apart from hepatomegaly. Liver function tests and full blood count were normal. She had an elevated level of carbohydrate antigen 19-9 (CA 19-9) which was initially 123ng/ml (NV: <37). The remaining serous neoplasmatic markers including carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA 125) and a-fetoprotein (AFP) were normal. Anti-echinococcal IgM and IgG antibodies and viral markers for hepatitis B and C were negative. Ultrasound (US) examination of the liver showed a cystic, well defined lesion of maximum diameter 14,3cm occupying liver segments IV and VIII. It also showed cholelithiasis. This finding led to a computer tomography (CT) scan that revealed a large 14x12cm well encapsulated cystic formation with internal septa and other cystic lesions of different density within it. (Figure 1). The lesion occupied liver segments II, III and IV and appeared to exceed the limits of the liver causing mild compression of surrounding structures. A radiological diagnosis of hydatid cyst was offered. The patient also had an upper GI endoscopy which showed a protruding wall in the anterior part of the antrum towards the lesser gastric

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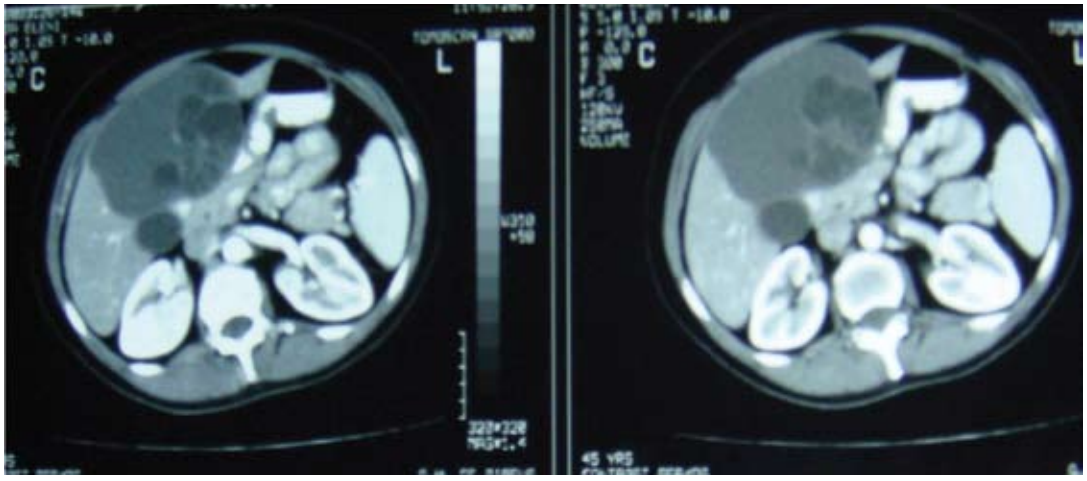

Figure 1. Abdominal CT showing a well demarcated multilocular thick walled cystic mass with internal septa. The diagnoses was hydatid cyst.

curvature with normal mucosa. No attempt to biopsy this area was made.

The patient underwent laparotomy under an extended right subcostal incision that revealed a large cystic formation with no macroscopic resemblance to a hydatid cyst. (Figures 2,3). A frozen section from the cystic wall was negative for carcinoma and the cyst was completely enucleated uneventfully (Figure 4). Cholecystectomy was also performed. No intra or postoperative blood transfusion was required. The postoperative course of the patient was uneventful and she was discharged one week later. Ten days after the procedure the CA 19-9 returned to normal (14,14ng/ml) and dropped even further 9ng/ml 1 month later. The histology report referred to a 12x7x3cm cystic lesion with a smooth wall lining. The epithelium was cuboidal or simple columnar with no atypia and had an underlying mesenchymal stroma resembling ovarian stroma. The final report was biliary cystadenoma. Six months after operation the patient is in excellent clinical health with no indication for abnormal biochemical heamatological or imaging findings.

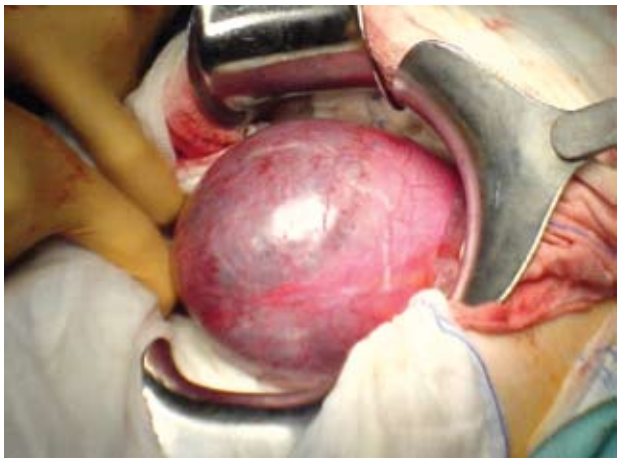

Figure 2. Macroscopic appearance of the cystic mass.

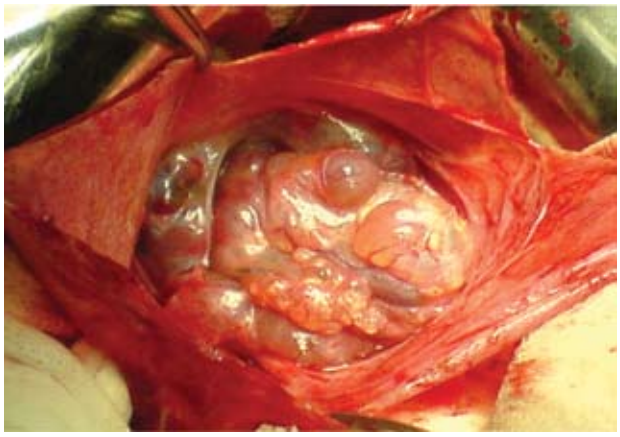

Figure 3. After opening the cyst wall many locules of variable size containing viscous fluid are seen.

DISCUSSION

The case described here had characteristics which fitted well with those of other reports (such as the female sex, typical findings on different imaging techniques) while others were almost unique, such as the elevated level of serum CA 19-9 (performed on the basis of general check-up) that made the patient to seek medical advise and the almost complete absence of symptoms especially from

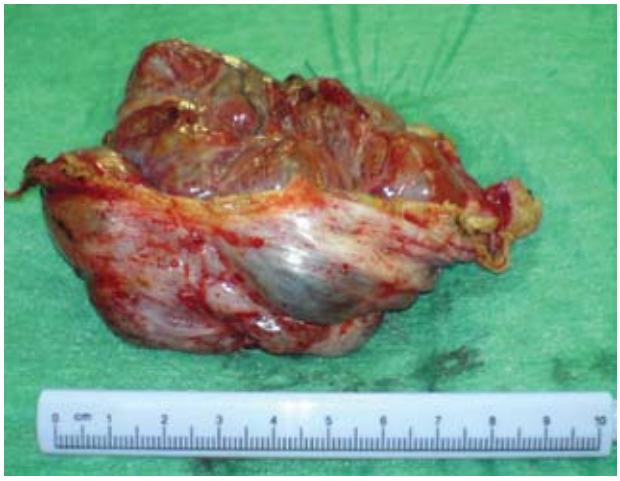

Figure 4. Multiloculated cystic neoplasm after complete enucleation.

the upper abdomen. The diagnosis was made on the operative table and confirmed histologically on the resected specimen. After the follow-up period of more that six months the patient is in complete health, with no signs of recurrence and with normal biochemical values including serum CA 19-9.

Billiary cystadenomas are rare benign but potentially malignant multilocular cystic neoplasms of the billiary ductal system accounting for less than 5% of cystic neoplasms of the liver[1-5,10]. Hepatobilliary cystadenomas can occur at any age but they are usually seen in middle-aged women.[2,3,5,9] They usually arise in liver (80-85%)[5,6,10-12,17], less frequently in extrahepatic bile ducts,[3,5,10-12,17] and rarely in gallbladder.[6,17]

The typical patient is a white female presenting with abdominal discomfort, swelling, gradual increase in abdominal girth and/or pain and a palpable mass.[1,2,5,12] Less frequently the patients have gastrointestinal obstruction leading to nausea and vomiting, dyspepsia, anorexia, weight loss or ascites.[2,14] Other less common symptoms include painful intracystic hemorrhage, rupture and fever from secondary infection[15]. Vena cava obstruction and thrombosis have also been reported[12]. Any patient presenting with recurrence of their liver cyst after surgical or radiologic treatment should be suspected of having a cystadenoma.

The cause of cystadenoma is not known. These cystic neoplasms, which involve primarily the hepatic parenchyma and occasionally the biliary tree including the gallbladder, may originate from a congenitally aberrant bile duct or directly from a primitive hepatobilliary stem cell.[1,3,12,16,17] Evidence does not support that cystadenoma are derived from ectopic ovarian tissue.[1,16] The almost exclusive female predominance suggests a strong hormonal influence.[16] There are reports of this tumour occurring in oral contraceptive users suggesting that these tumours are sensitive to estrogen and that estrogen containing oral contraceptives may serve as tumour promoters.[18]

Histologically billiary cystadenomas are true proliferative epithelial tumors.[2] They are usually large multiloculated with internal septation and are surrounded by a dense cellular fibrostroma.[2,6] A single layer of biliary type cuboidal- to- tall columnar, non ciliated and mucin secreting epithelial cells with papillary projections lines the cyst wall. They usually contain clear mucinous fluid.[3,12] Bloody fluid often signifies a malignant component.[2] Rarely the fluid within the cyst may be bilious, purulent, proteinaceous, gelatinous.[6] The septa may show calcification. Histologically cystadenomas can be divided into two subgroups that are distinguished by presence or absence of mesenchymal (ovarian like) stroma between an inner epithelial lining and an outer connective tissue capsule.[1,6,15] Cystadenomas with mesenchymal stroma (as in our case) occur exclusively in women, while cystadenomas without mesenchymal stroma but with hyaline stroma arise in both men and women.[1,6,16] Cystadenomas with mesenchymal stroma is regarded a precancerous lesion, but the type without mesenchymal stroma seems to undergo malignant degeneration much more frequently.[20,21] Patients with cystadenoma with mesenchymal stroma have a good prognosis whereas the prognosis of cystadenomas without mesenchymal stroma is poor, especially in men.[5,6,16]

Differential diagnosis includes simple liver cysts, parasitic cysts (particularly hydatid cyst), haematomas, post traumatic cysts, liver abscesses, polycystic diseases and neoplasmatic lesions such as biliary cystadenocarcinoma, metastatic ovarian or pancreatic adenocarcinoma, cystic primary primary hepatocellular carcinoma, cystic cholangiocarcimoma and hepatobiliary mesenchymal tumours such as biliary leiomyoma, adenomyoma and primary hepatic leiomyosarcoma.[2,6,10] Pre- and intraoperative diagnosis of biliary cystadenomas and cystadenocarcinomas can be very difficult and differentiation between them can be safely done only after histopathologic examination.[1,3,6,7,19,21] Special attention should be paid in differentiating cystadenoma from liver hydatid cyst especially in countries with high incidence since its imaging features are similar to those of cystadenoma, as in our patient. Antiechinococcus and antiamoebic serologic tests, estimation of CA19-9, CEA, and AFP levels, general evaluation of liver and renal status as well as abdominal ultrasound, CT and MRI should be performed.[2,6]

Serum level of CA 19-9 may be elevated and is a valuable marker in the diagnoses and monitoring of postoperative follow up since it has been reported by several authors to return to normal after complete resection[2,15,19,22,23] (as was evident in our patient). Normal levels of CA 19-9 does not rule out biliary cystadenoma [6,15]. CEA and AFP are usually normal.[17]

Cystic fluid analysis for CEA and CA19-9 can be very helpful in differentiating cystadenoma or cystadenocarcinoma from other hepatic cystic lesions.[15,24] High levels of CA 19-9 and CEA can be encountered in cystic fluid or in epithelial lining of biliary cystadenomas and biliary cystadenocarcinomas.[1,6,15,24,25] These elevated tumor markers give a clear indication of the neoplasmatic nature and biliary origin of these cysts and distinguish them from simple and echinococcal cysts.[1,6,15,23] The level of elevation in no way allows one to differentiate between cystadenoma and cystadenocarcinoma.[15] Indeed when a cystadenocarcinoma is suspected one must always weigh the relative risk of needle aspiration and tumour seeding versus proceeding straight to surgery.[15] Pleural and peritoneal dissemination of tumour cells caused by aspiration has been reported[26,27]. Although frozen sections may be helpful in differentiation of biliary cystadenoma and cystadenocarcinoma from other hepatic cystic lesions[6,28] they are not useful due to their inability to rule out cystadenocarcinoma.[6,16,26] Only careful histopathologic examination of the resected specimen constitutes a safe diagnostic modality of biliary cystadenoma and cystadenocarcinoma and can detect a malignant degeneration of a cystadenoma.[6]

Diagnosis and differential diagnosis of cystadenomas from other hepatic cystic liver lesions is mainly based on abdominal US, CT and MRI. Ultrasonography has proven very useful as an initial investigation as it outlines the anechoic mass with thin internal septa that are highly echogenic.[10,15] Some internal echoes may represent papillary growth instead of septation.[15] The tumour usually appears well demarcated, thick walled, non calcified, globular or ovoid.[2,6,10,29] Dilatation of intrahepatic or extrahepatic bile ducts may also be seen. On Doppler US examination vascular flow can be detected in the lesion.[30] Preoperative US assessment is always performed but cannot replace the diagnostic value of CT that can determine the size, morphology, anatomic relation to surrounding structures, particularly major vessels, of the lesion.[4,6] CT arteriography can demonstrate the tumour vascularity. On CT cystadenomas are usually seen as well demarcated lesions with contrast enhanced walls or septae.[15,30] Other features in CT include low density well defined lobulated, multilocular thick walled cystic masses[10,13,14,30,31]. CT may sometimes demonstrate dilatation of intrahepatic or extrahepatic bile ducts. Rarely course calcification along the wall of septa in a multilocular cystic mass indicate a more likely diagnoses of cystadenocarcinoma.[30,31] All the above features are essential for differentiating cystadenoma from other cystic liver lesions, but due to the rarity of the disease a preoperative diagnosis is rarely suspected, and in many cases it can be misdiagnosed as a hydatid cyst due to many common radiological features.

In MRI, on both T1 and T2 weighed images, the cystic spaces have variable signal intensity depending on their protein content and the presence or absence of hemorrhage[30]. MRI is a useful tool for the diagnosis and differentiation of cystadenoma while combination with MRCP is even more useful.[32] MRI may provide further information concerning the nature of the fluid in the cyst, blood versus mucin.[16]

Preoperative assumption that the lesion is benign based on US, CT and MRI findings is not safe and therefore not recommended.[26] The presence of irregular thickness of the wall, mural nodules or papillary projections indicates the possibility of malignancy.[4,6,10,29] Changes of the cyst wall may also suggest malignant transformation.[33] Hypervascularity of mural nodules on CT during arteriography may also indicate malignancy.[33] Angiography may be helpful both in clarifying the hepatic arterial anatomy and in differentiating cystadenocarcinoma from benign cystadenoma but seems not essential while the respectability of the tumor is assessed[6]. Imaging the intrahepatic bile ducts with endoscopic retrograde cholangiopancreatography (ERCP) or intraoperative cholangiography may be useful if a communication is suspected. ERCP is especially important if the patient is jaundiced.[6,15] Core needle biopsy for diagnoses risks dissemination of tumor cells and is not recommened.[15,26,27]

Because of the malignant potential and recurrence risk, treatment of choice must be radical excision. If a cystadenoma is suspected, or has been diagnosed, surgery is indicated even in asymptomatic patients since cystadenoma and cystadenocarcinoma can not be reliably differentiated based on radiologic and macroscopic criteria.[1,3,5-7,26] Partial excision and drainage ensure recurrence.[34] The extent of resection remains to be determined since lobectomy,[13,35] as well as wedge resection,[24] and enucleation,[12,24,36] have been reported.

In cases of communication of an intrahepatic cystadenoma with the biliary tree, biliary fistula should be confirmed and when identified, resection of the tumor should

be supplemented with suture closure of the fistula.[6,33] In treatment of extrahepatic cystadenomas, resection of the tumor should be supplemented with resection of the affected bile duct and billioenteric anastomoses.[6] Fenestration and complete fulguration of the cystic bed has also been reported in the literature as a successful treatment option but this remains yet to be confirmed whether it is indeed successful.[37] Billiary cystadenomas have historically been treated by marsupialization, internal Roux en Y drainage, aspiration, sclerosis or partial resection.[37] All of these methods have been associated with high rates of complications including sepsis, rupture, haemorrhage, continued growth and progress to malignancy.

Benign billiary cystadenomas are believed to transform to cystadenocarcinomas even decades after partial resection although few such lesions have been reperted.[6,16,21] Cystadenomas should therefore be appreciated as premalignant lesions.[3,6,15,21,33] Furthermore since cystadenoma cannot be easily differentiated preoperatively or intraoperatively from cystadenocarcinoma total surgical resection should always be considered[1,3,6,7,15,19,37]. Besides hepatic resection, complete enucleation is a safe and effective treatment.[15,17,37] Moreover techniques such as aspiration, fenestration, internal drainage, intratumoral sclerosant application or partial resection have disappointing results since recurrence rate is extremely high.[2,6,12]

The prognoses of completely removed billiary cystadenomas is excellent, recurrence is rare[1,2,5,6,37]. In addition cystadenocarcinomas may not show aggressive clinical behavior, and usually appear to have a slower growth rate and less frequent metastases or local invasion than other hepatic malignant neoplasms, such as hepatocellular carcinoma, cholangiocarcinoma and ovarian or pancreatic cystadenocarcinoma[6]. When treated with radical excision they also have good prognoses, particularly those with mesenchymal stroma, unless the tumor invades the adjacent liver tissue or neighboring organs, or metastases are present.[26] Cystadenocarcinomas in men which are not associated with mesenchymal stroma have worse prognosis, even after complete excision.[16]

In conclusion, the differential diagnoses of any cystic lesion in the liver should always include cystadenoma. When the diagnosis is unclear serum CA 19-9 and cyst fluid analysis for CEA and CA 19-9 may prove useful. The inability to preoperatively differentiate billiary cystadenocarcinoma, the high possibility of recurrence after palliative procedures and the potential of malignant transformation makes the treatment of choice to be complete excision. Besides hepatic resection, complete enucleation is a safe and effective treatment. Long term good outcomes are expected with total ablative treatment.

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