J Gastroenterol 1996; 31:732–736

Journal of Gastroenterology

Case report

Mucinous biliary cystadenoma with mesenchymal stroma: Expressions of CA 19-9 and carcinoembryonic antigen in serum and cystic fluid

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Abstract: A case of mucinous biliary cystadenoma with mesenchymal stroma (CMS tumor) in a 64-year-old woman is reported. The patient presented with acute abdominal pain and a palpable mass in the upper abdomen. Computed tomography and abdominal sonography showed characteristic multilocular cysts in the left lobe of the liver. Serum CA 19-9 was elevated to 108 U/ml with normal carcinoembryonic antigen (CEA) and alpha-fetoprotein (AFP) levels. The levels of CA 19-9 and CEA in the cystic fluid were high at 7430 U/ml and 576 ng/ml, respectively. The serum CA 19-9 returned to 35 U/ml 4 weeks after tumor resection. These corresponding findings of both tumor markers in the serum and cystic fluid imply that (1) CA 19-9 and CEA both exist in the epithelial component of CMS tumors as evidenced by immunohistochemical stain, (2) serum CA 19-9 is a valuable marker in the diagnosis and monitoring of CMS, and (3) in cystic fluid, there are more significantly high levels of CA 19-9 in CMS compared with levels in simple cyst and polycystic liver disease. Therefore, measurement of CA 19-9 in cystic fluid and serum may be helpful in the differential diagnosis of hepatic cystic lesions.

Key words: cystadenoma, liver, mesenchymal stroma, carcinoembryonic antigen, CA 19-9

Introduction

Biliary cystadenoma is a rare cystic, multiloculated tumor of biliary origin.[1–5] Of the cystadenomas, 83% are intrahepatic, and they less commonly involve the extrahepatic bile duct or gallbladder.[2] In 1985, Wheeler and Edmondson described two distinct classes of biliary cystadenoma based on the presence or absence of mesenchymal stroma.[6] One was "cystadenoma" that was devoid of mesenchymal stroma and was predominant in males. The second was composed of intermediate stroma components, referred to as "cystadenoma with mesenchymal stroma" (CMS) which was prevalent in females (100% of cases were females in Wheeler's report). Biliary cystadenoma with mesenchymal stroma (CMS tumor) is a distinct clinicopathological entity.[6] CMS tumors are usually benign in nature, but have potential for malignant progression. Preoperative evaluation depends on characteristic imaging findings, especially those of abdominal ultrasound and computed tomography (CT), but they are not definitive diagnostic tools. Elevated serum CA 19-9 and its presence in the epithelial component of CMS tumor were reported by Thomas.[7] These indicated that the determination of serum CA 19-9 may be useful in clinical diagnosis and management of CMS tumors. Therefore, we studied two tumor markers (CA 19-9 and CEA) in serum and cystic fluid of the tumors. We discuss here the correlation of clinical, radiological, and pathological findings.

Case report

A 64-year-old woman was presented with abdominal pain of ten days' duration. On examination, a protruding large mass was found in the upper abdomen. The patient reported no liver disease, abdominal trauma, toxin exposures, or oral medication. Routine hematological and biochemical tests were normal. Serum level of carcinoembryonic antigen (CEA) was 0.67 ng/ml (EIA, Abbott Laboratories, IL, USA; reference range <5 ng/ml) and alpha-fetoprotein (AFP) was undetectable (EIA, Abbott Laboratories, reference range <7 IU/ml). Nevertheless the serum level of CA 19-9 was notably high at 108 U/ml (IRMA, CIS Bio-international, France; reference range <37 U/ml). Ab-

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(Received June 16, 1995; accepted Jan. 26, 1996)

dominal sonography showed a multiple hypoechoic cyst with internal septa in the left lobe of the liver (Fig. 1). Abdominal CT revealed a multiloculated cystic mass with enhanced soft tissue component at the left lobe of the liver (Fig. 2) There was also a gallstone visible in the gallbladder. Subsequently, celiac and selective proper hepatic angiography showed a very large hypovascular mass in the left medial segment of the liver (Fig. 3). Therefore, an exploratory laparotomy was performed with the expectation of biliary cystadenoma.

At operation, an encapsulated multilocular cystic mass measuring about $10 \times 8 \times 7$ cm was discovered in the left medial segment of the liver. Complete left lobectomy and cholecystectomy was done. Grossly, the mass was generally lobulated with a smooth surface and delicate vasculature externally. The internal surface of the cyst had a smooth lining in the cystic wall with some trabeculations. The cystic mass contained about 400 ml of yellowish, turbid, mucinous fluid (Fig. 4). Tumor markers of cystic fluid were measured for CEA, AFP,

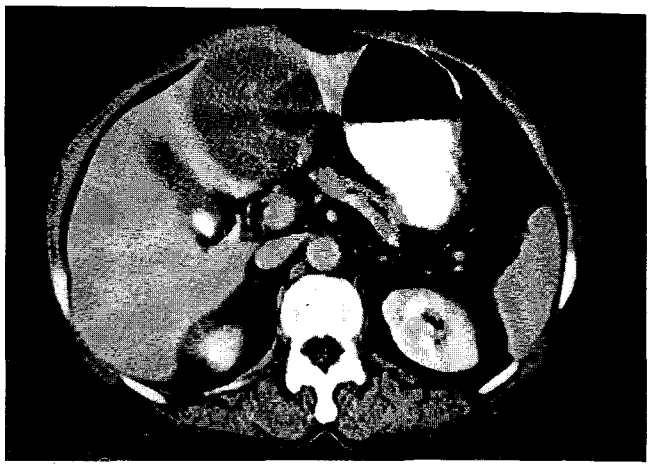

Fig. 2. Enhanced computed tomography scan of upper abdomen demonstrates a well-circumscribed, ovoid, low-density mass with multiple internal septa in the left medial segment of the liver. Note gallstone in gallbladder

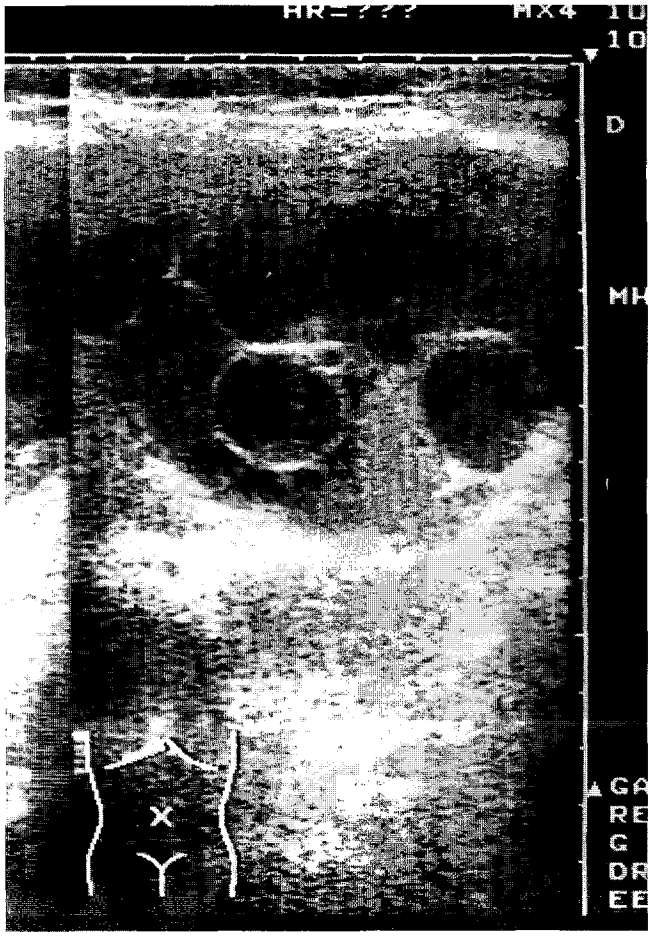

Fig. 1. Abdominal sonogram shows a multiloculated cystic mass comprised of several hypoechoic loculi with internal septa in the left lobe of the liver

Fig. 3. Subtraction angiogram via the proper hepatic artery reveals a huge hypovascular mass (*arrowheads*) in the left medial segment of the liver

Fig. 4. Cut surface of resected specimen of the liver reveals a well-defined multiloculated cystic mass with several septa. Note the smooth trabeculated interior of the loculi

and CA 19-9. The levels of CA 19-9 and CEA in the cystic fluid were significantly elevated at 7430 U/ml and 576 ng/ml, respectively. However, the alpha-fetoprotein level in the cystic fluid was negligible as was that in the serum. On microscopic examination, the inner layer of the cyst was lined by a single layer of columnar to cuboid epithelium, and the intermediate layer was composed of moderately dense mesenchymal stroma interposed between an inner epithelial lining and an outer connective tissue layer (Fig. 5). Mucinous biliary cystadenoma with mesenchymal stroma of the liver was diagnosed. Immunohistochemical analysis revealed the presence of CA 19-9 (histoCIS CA 19-9TM, CIS Bio International) (Fig. 6) and CEA (Dakopatts Anti-CEA, Denmark) (Fig. 7) in the epithelial component of the tumor. The patient recovered uneventfully and was discharged from the hospital 2 weeks postoperatively. Four weeks postoperatively, her serum CA 19-9 dropped from 108 U/ml to 35 U/ml. At the 1-year follow-up, the patient was well and there was no clinical evidence of recurrence.

Discussion

Biliary cystadenoma is a rare neoplasm derived from the bile duct. It comprises only 4.6% of intrahepatic cysts of biliary duct origin. Of the intrahepatic cystadenomas, 50% are in the right lobe, 29% in the left lobe, and 16% in both lobes.[2] The collective series of biliary cystadenomas show a marked predominance in women, with a ratio of 4:1.[8] Approximately two-thirds of the patients are 40 years old or older, and this condition is rare in children.[9] Cystadenomas vary markedly in size, ranging from 1 to 40 cm in diameter. Lesions in the

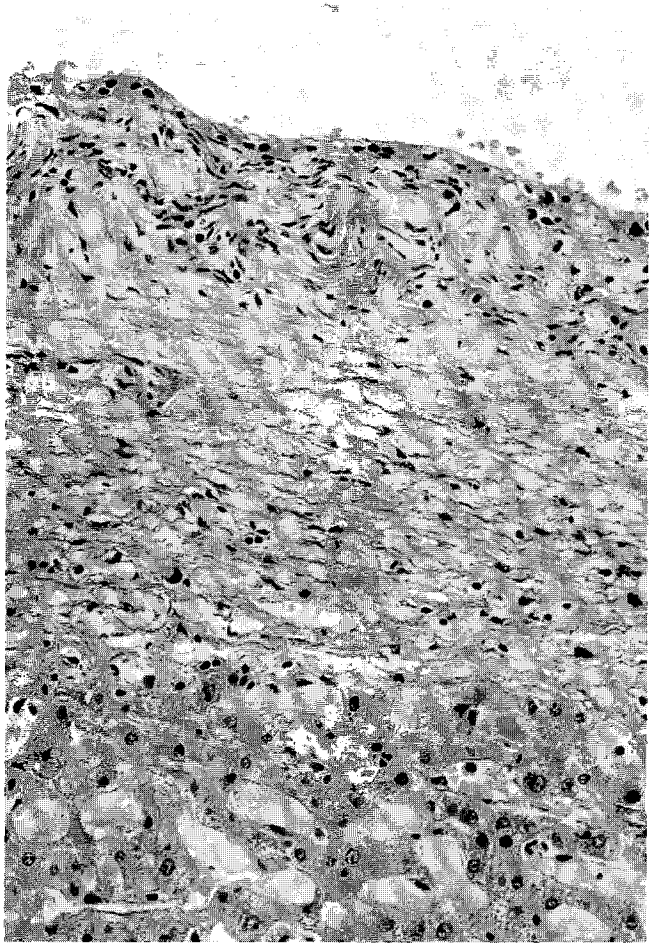

Fig. 5. Photomicrograph of cystadenoma with mesenchymal stroma (CMS) (*from top to bottom*): inner layer–columnar epithelial lining, intermediate layer–subepithelial stroma, outer layer–connective tissue, liver tissue (H&E, × 200)

liver and gallbladder are usually large, and only few of those reported measured less than 10 cm. Clinical manifestations of biliary cystadenoma are not specific. Symptoms always reflect the expansile nature of intraabdominal masses. Abdominal pain and masses commonly occured in about 80% of patients, often of two or more years' duration.[10] Cholangitis and sepsis follow. Obstructive jaundice was also found in some cases.

Wheeler and Edmonson stated that CMS tumor invariably consisted of three layers: (1) the inner layer of the cyst lined by a single layer of columnar to cuboid epithelium, (2) the intermediate layer of cellular subepithelial stroma composed of spindle cells (mesenchymal stroma), and (3) the outer layer of connective tissue with hyaline changes. The hallmark of a cystadenoma is the presence of columnar-lined papillary infolding in multilocular cysts. Papillary infolding of epithelium may form septa that divide the cyst into

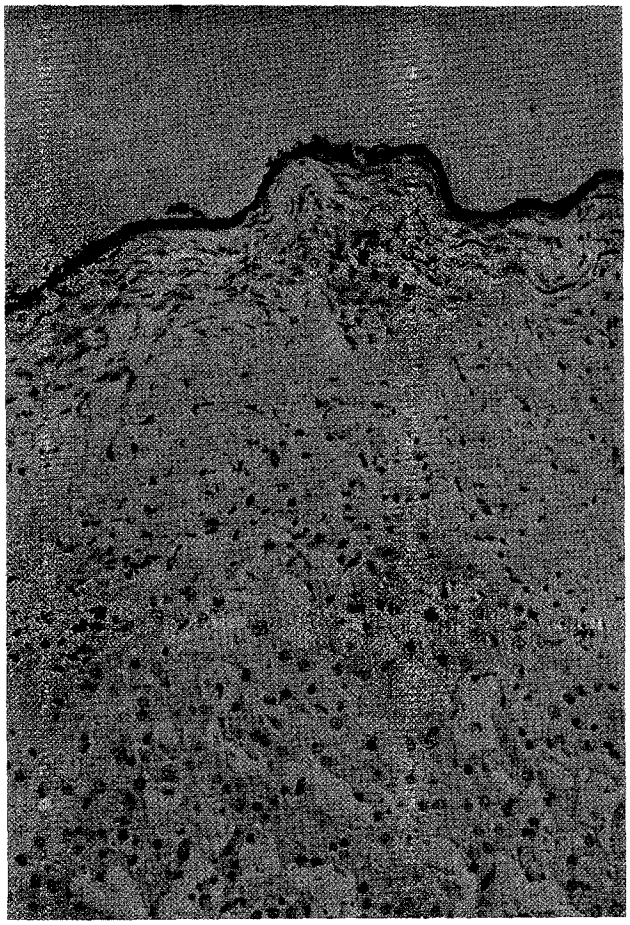

Fig. 6. Immunohistiochemical staining for *CA 19-9* shows a positive cytoplasmic reaction in the epithelial cell component of CMS. ×200

multiloci. The contents in these lesions can be clear, mucinous, gelatinous, purulent, hemorrhagic, or bile-stained, and can be variable in color and composition in each loculus. The etiology of cystadenoma seems to be neoplastic but not environmental or congenital. Wheeler and Edmondson hypothesize that these tumors arise from ectopic remnants of embryonic bile ducts.[6-11]

Biochemical tests in this case revealed, high serum CA 19-9 (108 U/ml) with normal alpha-fetoprotein and CEA, which is consistent with a previous study.[7] A 7430 U/ml level of CA 19-9 in cystic fluid corresponds well with a high level of 108 U/ml in the serum. Immunohistochemical analysis revealed the presence of CA 19-9 and CEA in the inner epithelial layer of the tumor. However, 576 ng/ml CEA in cystic fluid seems not high enough to raise the serum level to diagnostic significance. After complete tumor resection, CA 19-9 returned from a preoperative level of 108 U/ml to a normal level of 35 U/ml in a 4-week period. In addition, we measured CA 19-9 levels of cystic fluid obtained from patients with a simple cyst (3 cases) and polycystic liver (2 cases). The results were 2.46 U/ml, 7.84 U/ml, and 2.02 U/ml in patients with a simple cyst, and 3.78 U/ml and 10.71 U/ml in patients with polycystic liver, respectively. Obviously, measurement of CA 19-9 in cystic fluid may be useful in differential diagnosis of CMS, simple cyst, and polycystic liver.

For cystic lesions of the liver, differential diagnoses include simple liver cyst, polycystic liver, liver abscess, echinococcal cyst, traumatic cyst, Caroli's disease, metastasis with cystic degeneration, biliary cystadenoma,

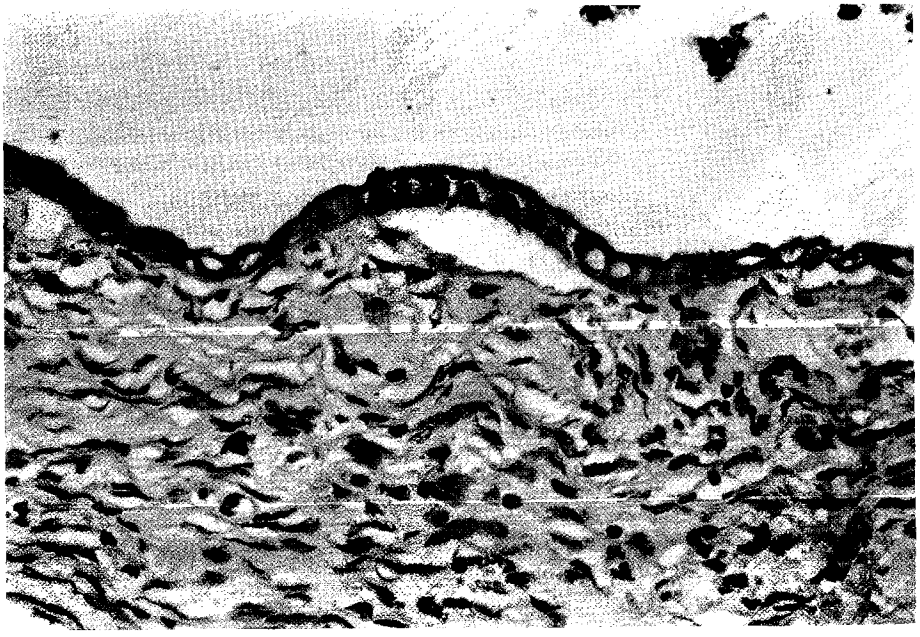

Fig. 7. Immunohistochemical staining for carcinoembryonic antigen shows a positive cytoplasmic reaction in the epithelial cell component. ×400

and cystadenocarcinoma. CT and ultrasound images provide a characteristic appearance in these lesions, but are not in themselves definitive diagnostic tools. The usual appearance of CMS on CT and ultrasound is a single, multilocular cystic mass with papillary excrescence and nodular thickening of internal septa.[12–17] There is heterogeneous echogenicity of contiguous mural loculi in biliary cystadenoma in contrast to unique echogenicity in simple liver cyst and polycystic liver. Liver abscess usually demonstrates an ill-defined cystic mass without the septa and multilocular appearance, and it is easily differentiated by clinical manifestations. Serologic study will help to diagnose echinococcal cyst lesions. Although serum CA 19-9 has proven useful in the diagnosis and management of patients with cancer of the pancreas, it has little value in normal subjects or in those with benign diseases except for two disorders—liver cirrhosis and acute cholangitis.[18] Both pancreatic disorders and biliary cystadenoma can elevate serum CA 19-9.

Biliary cystadenocarcinoma appears to arise from benign cystadenoma.[19] When malignant transformation occurs, it takes place from the epithelial layer of CMS as papillary cystadenocarcinoma that is classified as type II (cystadenocarcinoma with cystadenoma) cystic adenocarcinoma of the liver, according to the new classification of the Liver Cancer Society of Japan (1991).[20] Unfortunately, it is still difficult to distinguish benign from malignant lesions by ultrasound, CT, or other imaging studies without histologic examination.[21] Diagnosis of cystadenocarcinoma has been confirmed by biopsy or aspiration cytology under ultrasound guidance. Although intraperitoneal dissemination caused by needle biopsy has been reported in cystadenocarcinoma,[17] fine-needle aspiration cytology may minimize these risks.[22]

In the collective literature, treatment of biliary cystadenoma has included aspiration, sclerosis, percutaneous drainage, marsupialization, internal drainage, and partial or total excision. Nine of fifteen cases of biliary cystadenoma had previous radiological or surgical interventions other than total excision, and they needed further definitive treatment for tumor recurrence or sepsis.[10] Therefore, any therapy short of total excision of cystadenoma leaves the patient at significant risk of tumor recurrence, secondary infection, sepsis, and possible malignant transformation. If the cystadenoma was more central or was large, enucleation was carried out 80% to 90% of the time with minimal loss of liver tissue and blood.[8] Many investigators strongly suggested total excision of the tumor as the choice of treatment, and demonstrated excellent results.

In summary, CMS is histologically distinct from other hepatic cystic lesions, and its occurrence correlates significantly with sex and age. Determinations of CA 19-9 in cystic fluid and serum may be useful in diagnosis and follow-up of CMS tumors.

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