

The Role of Tumor Markers and Cytology in Hepatic Cysts with Malignant Potential: A Self Controlled Study

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| Background | Preoperative differentiation between benign and malignant hepatic cysts with fine needle aspiration is poorly sensitive or specific. The additional value of evaluating cyst cytology carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) is poorly understood. |
| Summary | A 78-year-old asymptomatic woman presented to us with elevated liver function tests for abdominal bloating, prompting a computed tomography (CT) scan that demonstrated obstruction of a left lateral section biliary pedicle associated with a giant 10 cm left lateral section cyst with an associated complex nodule, concerning for malignancy. Additionally, she had a giant 22 cm cyst in the right liver with associated posterior section atrophy. We performed a laparoscopic right anterior section cyst aspiration and unroofing, and a laparoscopic hand assisted left lateral hepatectomy. Final pathology revealed that the left liver cyst was a poorly differentiated adenocarcinoma, pT2aN1 with an associated CEA of >900 and CA19-9 of 174,602; the right liver cyst was negative for carcinoma with an associated CEA of 4.1 and CA19-9 of 37,339. This case suggests that an elevated CEA may have better correlation than CA19-9 for malignancy in hepatic cystic lesions. |
| Conclusion | Accurate diagnosis of benign and malignant hepatic cysts remains problematic. This self-controlled case provides a unique insight into the serologic tumor marker differences in benign and malignant hepatic cysts with cystic CEA and CA19-9, suggesting a potential role for elevated cystic fluid CEA in the evaluation of malignant hepatic cysts. |
| Keywords | Biliary cyst, cholangiocarcinoma, cytology, CEA, CA19-9 |

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Case Description

A 78-year-old asymptomatic woman presented to us with elevated liver function tests on laboratory workup of abdominal bloating, prompting a computed tomography (CT) scan that demonstrated obstruction of the left lateral section biliary with a very complex nodule within a giant 22 cm left lateral section cyst, concerning for cholangiocarcinoma versus cyst adenocarcinoma (Figure 1).

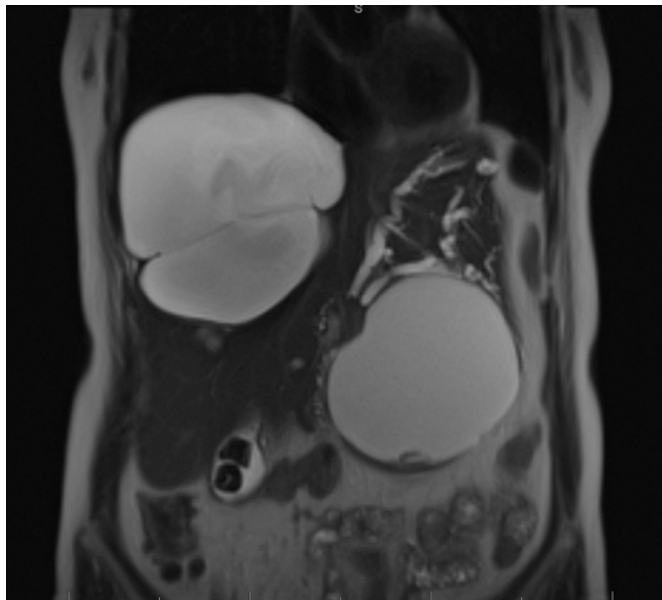


Figure 1. MRI demonstrating right and left hepatic cysts, left hepatic cyst with associated mass (arrow) resulting in biliary obstruction and dilation.

Additionally, she had a large cyst in the right liver with associated posterior section atrophy. Staging workup was negative for metastatic disease. We obtained liver volumetrics and found that she would have adequate liver volume to undergo a left hepatectomy. We performed a diagnostic laparoscopy without evidence of malignancy, then proceeded with a laparoscopic right anterior section cyst aspiration and unroofing, and a laparoscopic hand-port assisted left lateral sectionectomy after aspiration of the cyst (Figure 2 and Figure 3).

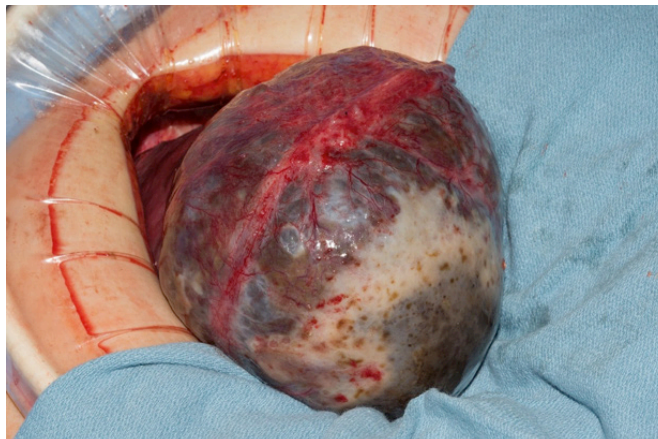


Figure 2. Left hepatic cyst after laparoscopic mobilization.

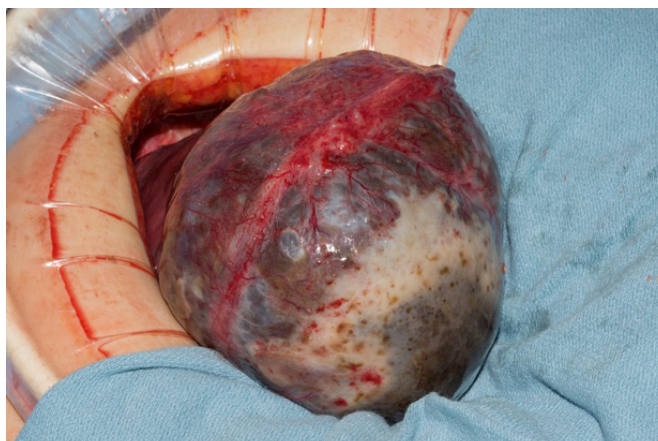


Figure 3. Aspiration of left hepatic cyst prior to resection of Segments 2 & 3.

The laparoscopic portion was performed for liver mobilization, then the hand-port was used to dissect the umbilical fissure and resect the left lateral section and the involved part of the left bile duct. The latter part was not done laparoscopically due to the lack of domain due to the cyst size. Final pathology revealed that the left liver cyst was a poorly differentiated pT2aN1 intrahepatic cholangiocarcinoma arising within a biliary cyst; this was not a cystadenocarcinoma due to the absence of ovarian type stromal tissue. Cystic fluid tumor markers for the malignant cyst demonstrated a carcinoembryonic antigen (CEA) of >900 and carbohydrate antigen 19-9 (CA19-9) of 174,602. The right liver cyst was negative for carcinoma, and demonstrated a CEA of 4.1 and CA19-9 of 37,339. Both cysts had negative cytology (Table 1). The patient convalesced well and was discharged on postoperative day four without complication.

| | CA 19-9 | CEA | Cytology | Pathology |
|------------------|---------|------|----------|------------------------------|
| Left liver cyst | 174,602 | >900 | Negative | pT2aN1 cholangiocarcinoma |
| Right liver cyst | 37,339 | 4.1 | Negative | Negative |

Table 1. Cyst fluid characteristics of left and right liver cysts (same patient)

Discussion

Hepatic cystic lesions represent a broad spectrum of disease entities, many of which may follow a benign course and remain asymptomatic.¹ Less than 5 percent of all cystic lesions of the liver are cystic neoplasms.² However, it is critical to be able to discriminate between benign and neoplastic cysts that may require specific treatment.

Cholangiocarcinoma (CCA) is a rare malignancy arising from the epithelial cells of the bile ducts, and accounts for approximately 10–25 percent of all liver cancers.³ CCAs are subdivided as intrahepatic, perihilar, or extrahepatic, which vary in clinical presentation, differential diagnosis, and prognosis. Intrahepatic cholangiocarcinoma (IHCC) represent approximately 20 percent of all cholangiocarcinomas,⁴ and have had an increasing incidence and mortality in recent decades.⁵ Curative resection remains the only effective treatment modality for CCA. The median survival of patients with IHCC who undergo surgery is six months, while the five-year survival for patients with IHCC who undergo resection is only 20–40 percent.³

Diagnostic evaluation includes a combination of imaging, endoscopy, cholangiography, and serologic tumor markers. While many tumor markers have been evaluated, serum CA19-9 and CEA have emerged as the most studied.³ Elevated serum CA19-9 >37U/mL has been associated with a higher incidence of metastases and poorer prognosis in cholangiocarcinoma, however the sensitivity and specificity for diagnosing IHCC is 62 percent and 63 percent, respectively.⁶ Additionally, serum CA19-9 may be falsely elevated in benign biliary disease or cholangitis.³ Serum

CEA has been associated with several gastrointestinal tract malignancies, including stomach, colon, pancreas, and CCA. In one large series tracking 333 patients with primary sclerosing cholangitis who developed CCA, serum CEA level >5.2 ng/mL was found to have a sensitivity and specificity of 68 percent and 82 percent, respectively.⁷ However, CEA has also been found to be elevated in nonmalignant conditions, including gastritis, peptic ulcer disease, diverticulitis, diabetes, and other conditions of inflammation.

Tumor markers of aspirated cyst fluid may offer additional insight, however there is a paucity of data on biliary cyst fluid aspiration. In one review of six patients with benign biliary cysts, cystic fluid showed more than 100-fold increase of cystic fluid CA19-9, arguing against its utility for detecting malignancy.⁸ In a review of 17 consecutive cystic lesions from 15 patients studying cyst fluid CEA, low levels (<5ng/mL) were found in benign, nonmucinous cysts and elevated levels (>600 ng/mL) were found in biliary cystadenomas, cystadenocarcinomas, and pseudocystic metastatic carcinomas, yielding a sensitivity of 100 percent and specificity of 94 percent, suggesting that cystic fluid CEA may help in the detection of malignant cystic liver lesions.⁹

From the literature on pancreatic cystic lesions, pancreatic cystic fluid CEA and CA19-9 have found to be elevated in malignant cysts.¹⁰ The sensitivity and specificity of CEA is 91.8 percent and 63.9 percent and of CA 19-9 were 81.3 percent and 69.4 percent, respectively.¹⁰ Cyst fluid CEA has been found to be helpful in discriminating mucinous from nonmucinous pancreatic cysts, but has not been able to aid in the differentiation between premalignant and

malignant cysts.^{11,12} Similarly, low pancreatic cyst CA19-9 levels (<37U/ml) suggest benign lesions, but elevated levels do not distinguish between premalignant and malignant lesions.¹⁰

Biliary cytology has a limited role in the diagnosis of CCA. In one study of 97 patients with cholangiocarcinoma, biliary cytology had only a modest sensitivity of 55 percent, with 100 percent specificity.¹¹⁻¹³ In a large study of 766 consecutive patients who underwent biliary drainage for obstructive jaundice due to CCA, cytology of the drained bile yielded a sensitivity of 24.7 percent.¹⁴ Factors that were found to be associated with a positive bile cytology included perihilar tumor location, tumor extent >20 mm, poorly differentiated grade tumor, and three or more samplings.¹⁴ This study did find that the addition of endobiliary forcep biopsy increased sensitivity to 77.9 percent, and therefore biliary cytology may have a role when combined with endobiliary biopsy.¹⁴ In our case, we found the cytology of the malignant biliary cystic lesion to be negative, supporting the limited role for biliary cytology alone.

Conclusion

Cholangiocarcinoma remains an aggressive malignancy with a poor prognosis. It is minimally responsive to chemotherapy and radiation, and surgical resection is currently the only effective therapy. CCA is difficult to diagnose, and there is no specific serologic biomarker for detection of CCA.³

Stratifying risk of malignancy in biliary cysts remains difficult, despite advances in non-invasive imaging modalities. Currently, our understanding for the role of biliary cyst aspiration is limited. However, there is data to suggest that cystic fluid CEA, but not CA19-9 may help to stratify the risk of malignancy. This self-controlled study provides a unique support for the value of cystic fluid CEA, but not CA19-9 in differentiating benign versus malignant cysts.

Lessons Learned

Accurate preoperative differentiation of benign versus malignant biliary cysts is challenging. Elevated biliary cyst aspiration CEA, but not CA19-9, may help to stratify high risk biliary cysts that should be resected.

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