Spontaneous rupture of a giant hepatobiliary serous cystadenoma: report of a case and literature review

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Abstract Hepatobiliary cystadenomas are rare cystic neoplasms that often occur in middle age women, and spontaneous rupture is extremely rare. The exact etiology of these tumors is unknown. Diagnosis is often delayed, while misdiagnosis and inappropriate treatment may result in unfavorable outcome. We report a case of hepatobiliary serous cystadenoma with mesenchymal stroma, initially misdiagnosed as simple hepatic cyst with intracystic hemorrhage. The rapid growth of the giant tumor leads to spontaneous rupture, almost turned into a life-threatening event. After emergency formal liver resection, the patient recovered well without recurrence during the 6-month follow-up period. We also reviewed the literature, proposed possible factors for the tumor's rapid growth, and discuss the current diagnostic and treatment modalities.

Keywords Hepatobiliary cystadenoma · Rupture · Spontaneous · Diagnosis · Therapy

Introduction

Hepatobiliary cystadenomas (HBCs) are rare, benign but potentially malignant cystic neoplasms of the hepatobiliary

system. Because of its rarity and similarity to other cystic liver lesions, diagnosis is often delayed and may result in inappropriate treatment, such as aspiration and fenestration, thus further causing unnecessary morbidity and mortality. The number of reported cases has been increasing due to the advances in imaging techniques and the frequent use of imaging studies. The characteristics of these lesions have been recognized gradually, but accurate diagnosis and proper management are still medical dilemmas.

Spontaneous rupture of hepatobiliary cystadenoma or cystadenocarcinoma is a very rare and potentially life-threatening complication, with very few cases reported in the English literature to our knowledge [1, 2]. Here we report this rare case to elucidate the possible factors that may promote the rapid growth of the tumor, and to discuss current diagnostic and treatment modalities.

Case report

A 42-year-old woman complained of vague abdominal pain and increased abdominal girth was referred to our clinic. No other signs or symptoms were noted except for a marked cystic mass in the abdomen to the level of umbilicus. Abdominal computed tomography (CT) scan revealed a low density giant cystic lesion occupying most of the left lobe, measuring $19 \times 29 \times 32$ cm. The lesion is irregularly shaped and encapsulated. The cystic wall is thickened with mural nodules and calcifications. The cystic wall, internal septations, and mural nodules showed slight enhancement after intravenous administration of contrast medium. Laboratory tests showed an elevation of CA-199–81.4 U/ml (0–37 U/ml), whereas α -fetoprotein (AFP), carcinoembryonic antigen (CEA) were within normal limits. Biochemical profiles were

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unremarkable. Viral markers for hepatitis B and C were negative.

The patient had a past history of schizophrenia and was on clozapine 300 mg/d for 9 years. An asymptomatic 3.8×2.7 cm cyst in liver was detected by ultrasound (US) 8 years prior to admission which gradually enlarged upon follow-ups. Three years prior to admission, she gave birth to a baby which was uneventful. The patient attempted suicide and jumped from a building 3 months after the delivery, causing pelvic fracture as well as contusion and laceration of liver. At the emergency room, abdominal CT scan showed a large cystic lesion with separations, approximately 7.4×12.1 cm. Simple hepatic cyst complicated with intracystic hemorrhage was suspected and she was treated conservatively and recovered. 2 years prior to admission, the cyst sized up to 16.4×22.7 cm on repeated abdominal CT.

The patient decided to pursue surgical treatment due to the newly onset discomfort associated with the hepatic lesion. After admission, she presented with sudden severe abdominal pain, dyspnea and tachycardia followed by decreased blood pressure and hypoxemia. Physical examination revealed abdominal tenderness and cyst rupture-induced anaphylactic shock or septic shock. The vital signs were unstable, and an emergency laparotomy was performed under a right transrectus incision, revealing a giant cyst (30 cm in diameter) located in the left lobe of the liver. A large amount of thick, bile-stained mucinous fluid spilled out into the peritoneal cavity. The surface of the cyst was dark red with abundant blood supply which was tightly adhered to the abdominal wall and adjacent organs. After careful dissection, a 2-cm rupture was found at the left bottom of the cystic lesion. A left lobectomy was performed and the entire cyst was removed successfully.

On pathologic examination, the resected specimen was a unilocular cyst filled with bile contents, measuring $29 \times 21 \times 10$ cm. The thickness of wall was 0.2–1.0 cm with intra-mural microcyst formation, ranging from 0.5 to 2.0 cm in size. Papillary projections, septa, calcification and hyaline degeneration of the stroma were seen in the cystic wall. Microscopically, the cyst was lined by columnar and cuboidal epithelium without atypia and had underlying dense cellular mesenchymal stroma, resembling ovarian stroma. Clusters of glandular cells with round nuclei and clear cytoplasm were identified in the cystic fluid. Immunohistochemical stains for estrogen receptor (ER), progesterone receptor (PR), smooth muscle actin (SMA), chromogranin A, synaptophysin, and Ki-67 were performed. The stroma cells showed strong and diffuse staining for ER, PR, and SMA. The epithelial lining of the cystadenoma contained scattered chromogranin and synaptophysin positive cells, representing the endocrine cells. The proliferation index by Ki-67 stain was very low (<1%).

The final pathology diagnosis was hepatobiliary serous cystadenoma.

The postoperative course was uneventful and the patient was discharged 2 weeks after the surgery. No evidence of recurrence was found during the 6-month follow-up period.

Discussion

Hepatobiliary cystadenomas are rare, benign cystic lesions which usually arise in the liver (80–85%) in the extrahepatic bile ducts and rarely in the gallbladder [3, 4]. Approximately 85–95% of the patients are women typically occurring in the fifth decade of life [5].

The exact etiology of HBCs remains unknown. Both congenital and acquired causes have been proposed. The tumor may arise from the ectopic remnants of primitive foregut sequestered within the liver or secondary to the obstruction of the congenitally aberrant bile duct, or directly from primitive hepatobiliary stem cells [6]. The development of the tumor as a reactive process to some local injuries had also been proposed [7]. In our case, the local injury may act as a promoter for the rapid growth.

The predilection for women suggests a role of strong hormonal influence. Immunohistochemical studies have revealed myofibroblastic phenotype and expression of progesterone and ERs, proposing a possible hormonal dependence of cystadenomas [8]. Our patient had taken oral clozapine for 9 years which is known to have an influence on prolactin generation, thus to affect the estrogen level. And her pregnancy might have further effects on hormonal levels. We confer a hypothesis that the oral drug, pregnancy and local injuries of the liver may all act as triggers for the rapid growth (28 cm of increase within 8 years).

Clinical manifestations may be associated with biliary obstruction, secondary bacterial infection or intracystic hemorrhage in some cases. In general, clinical manifestations are considered less reliable in the diagnosis of HBCs.

Elevated CA 19-9 and CEA can be detected in the cystic fluid or the epithelial lining of biliary cystadenomas, particularly in those with mesenchymal stroma [9]. But normal level of CA 19-9 does not necessarily rule out HBCs. Imaging studies by US, CT and MRI play an important role in recognizing the lesion. Characteristic features include sharp demarcation, irregularly thickened wall, calcifications, internal septa and mural papillae, as shown in our case. US is more sensitive for detecting septations and mural nodules, whereas CT or MRI is essential to determine the size, morphology and anatomic relationship to the surrounding structures, particularly to the major vessels. MRI may also improve tissue characterization because of its high contrast resolution. Signal intensity may vary as it

depends on the nature of cyst fluid, which may be serous, mucinous or hemorrhagic [10]. Levovist ultrasonography imaging could play an important role in the differential diagnosis from hemorrhagic simple cyst by demonstrating the vascularity of the visualized intracystic structures [11]. Despite these features, differential diagnosis between hepatobiliary cystadenoma and hepatobiliary cystadenocarcinoma is still difficult.

Although there are reports of cystadenocarcinomas arising from cystadenomas diagnosed by percutaneous fine needle aspiration cytology, the accuracy of the procedure is limited [12]. It is not generally recommended in cases of overt or suspected cystadenocarcinoma, particularly when surgery is planned.

The differential diagnoses include simple cysts, parasitic cysts, post-traumatic cysts, cystic degeneration of liver neoplasm [4, 6]. The most challenging one is hemorrhagic cysts where US may mistaken the internal clots for papillary nodules and irregular septa. The patient we reported here was misdiagnosed as hemorrhagic cyst after the trauma and proper treatment was delayed.

Due to the difficulties in distinguishing cystadenoma from cystadenocarcinoma preoperatively and its malignant potential, surgical resection is recommended even in asymptomatic patients. Hepatic resections are considered the choice of treatment. Besides, radical cystectomy is also a safe and effective treatment. Good outcomes after long term follow-ups are expected with total ablative treatment [13]. With advancement of technique, laparoscopic surgery plays a growing role in the treatment of carefully selected patients with liver lesions and promising results have been achieved. [9] Incomplete excision will almost certainly result in a higher rate of recurrence and the risk of malignant transformation [14]. Any recurrence of a liver cyst after surgical or radiologic treatment should be suspected of cystadenoma [13]. Furthermore, rapid growth within a short time is highly suspicious for cystadenoma or cystadenocarcinoma.

Intraoperative biopsy and rapid frozen sections are essential although they are not 100% accurate [10]. If the biopsy confirms cystadenoma, complete excision is necessary. Incidental finding of a cystadenoma during surgery for other clinical indications demands a complete surgical resection of the tumor [15].

As large tumor with papillary projections, extensiveness of sampling and number of histopathology sections should be done to avoid local canceration. Special histochemical stains such as ER, PR, SMA, Ki-67 stains may be helpful for confirming the diagnosis.

Biliary cystadenoma are classified according to the epithelial lining, the rare serous type as in our case and the more common mucinous type. Histologically, cystadenomas can also be divided into two subgroups according to

the presence of mesenchymal (ovarian like) stroma between the inner epithelial lining and the outer connective tissue capsule. Cystadenoma with mesenchymal stroma as in our case is regarded as a precancerous lesion, occurs exclusively in women, and implies a good prognosis [16]. However, cystadenomas absent of mesenchymal stroma show similar incidence in both sex that tend to occur in older patients which seem to undergo malignant transformation much more frequently [17], implying poor prognosis, especially in male patient even after complete excision [4, 10].

In conclusion, the advances in imaging techniques allow better recognition of this entity. Cyst fluid CA 19-9 and CEA levels can serve as an adjunctive preoperative procedure, but not a tumor marker of adequate accuracy. Any diseases or drugs that influence hormone level as well as local injuries may serve as factors for tumor's growth, and rapid growth within a short time is highly suspicious for cystadenoma or cystadenocarcinoma. Laparotomic or laparoscopic complete excision is the treatment of choice to ensure a better prognosis. In case of large cysts, operation should be performed as early as possible to avoid life-threatening ruptures.

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